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(54) Pyrazolopyrimidinone antianginal agents

Pyrazolopyrimidone als Wirkstoffe gegen Angina

Pyrazolopyrimidones comme agents antiangineux

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(56) References cited:
EP-A- 0 201 188 **EP-A- 0 463 756**

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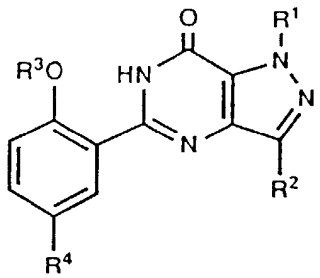
Description

The invention relates to a series of pyrazolo[4,3-d]-pyrimidin-7-ones, which are potent and selective inhibitors of cyclic guanosine 3',5'-monophosphate phosphodiesterase (cGMP PDE), having utility in a variety of therapeutic areas including the treatment of various cardiovascular disorders such as angina, hypertension, heart failure and atherosclerosis.

The compounds of the invention exhibit selectivity for inhibition of cGMP PDEs rather than cyclic adenosine 3',5'-monophosphate phosphodiesterases (cAMP PDEs) and, as a consequence of this selective PDE inhibition, cGMP levels are elevated, which in turn can give rise to beneficial anti-platelet, anti-neutrophil, anti-vasospastic and vasodilatory activity, as well as potentiation of the effects of endothelium-derived relaxing factor (EDRF) and nitrovasodilators. Thus the compounds have utility in the treatment of a number of disorders, including stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, conditions of reduced blood vessel patency e.g. post-percutaneous transluminal coronary angioplasty (post-PTCA), peripheral vascular disease, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma, and diseases characterised by disorders of gut motility, e.g. irritable bowel syndrome (IBS).

European patent application EP-A-0201188 discloses certain pyrazolo[4,3-d]pyrimidin-7-ones as adenosine receptor antagonists and PDE inhibitors, useful in the treatment of cardiovascular disorders such as heart failure or cardiac insufficiency. However these compounds are neither particularly potent PDE inhibitors, nor are they reported to be selective inhibitors of cGMP PDE.

The compounds of the present invention have the formula (I):



(I)

wherein

R^1 is H; C_1-C_3 alkyl optionally substituted with one or more fluoro substituents; or C_3-C_5 cycloalkyl;

R^2 is H, or C_1-C_6 alkyl optionally substituted with one or more fluoro substituents or with C_3-C_6 cycloalkyl;

R^3 is C_1-C_6 alkyl optionally substituted with one or more fluoro substituents or with C_3-C_6 cycloalkyl; C_3-C_5 cycloalkyl; C_3-C_6 alkenyl; or C_3-C_6 alkynyl;

R^4 is C_1-C_4 alkyl optionally substituted with OH, NR^5R^6, CN, $CONR^5R^6$ or CO_2R^7; C_2-C_4 alkenyl optionally substituted with CN, $CONR^5R^6$ or CO_2R^7; C_2-C_4 alkanoyl optionally substituted with NR^5R^6; hydroxy C_2-C_4 alkyl optionally substituted with NR^5R^6; (C_2-C_3 alkoxy)C_1-C_2 alkyl optionally substituted with OH or NR^5R^6; $CONR^5R^6$; CO_2R^7; halo; NR^5R^6; $NHSO_2NR^5R^6$; $NHSO_2R^8$; or phenyl or heterocyclyl either of which is optionally substituted with methyl;

R^5 and R^6 are each independently H or C_1-C_4 alkyl, or together with the nitrogen atom to which they are attached form a pyrrolidinyl, piperidino, morpholino, 4-(NR^9)piperazinyl or imidazolyl group wherein said group is optionally substituted with methyl or hydroxy;

R^7 is H or C_1-C_4 alkyl;

R^8 is C_1-C_3 alkyl optionally substituted with NR^5R^6;

and

R^9 is H; C_1-C_3 alkyl optionally substituted with phenyl; hydroxy C_2-C_3 alkyl; or C_1-C_4 alkanoyl;

and pharmaceutically acceptable salts thereof.

In the above definition, unless otherwise indicated, alkyl groups having three or more carbon atoms may be straight or branched chain. In addition alkenyl or alkynyl groups having four or more carbon atoms, or alkoxy groups having three carbon atoms, may be straight or branched chain. Halo means fluoro, chloro, bromo or iodo, whilst heterocyclyl is selected from thienyl, pyridyl, pyrazolyl, imidazolyl, triazolyl, oxazolyl, thiazolyl or pyrimidinyl.

The compounds of formula (I) may contain one or more asymmetric centres and thus they can exist as enantiomers

or diastereoisomers. Furthermore certain compounds of formula (I) which contain alkenyl groups may exist as cis- or trans-isomers. In each instance, the invention includes both mixtures and separate individual isomers.

The compounds of formula (I) may also exist in tautomeric forms and the invention includes both mixtures and separate individual tautomers.

Also included in the invention are radiolabelled derivatives of compounds of formula (I) which are suitable for biological studies.

The pharmaceutically acceptable salts of the compounds of formula (I) which contain a basic centre are acid addition salts formed with pharmaceutically acceptable acids. Examples include the hydrochloride, hydrobromide, sulphate or bisulphate, phosphate or hydrogen phosphate, acetate, benzoate, succinate, fumarate, maleate, lactate, citrate, tartrate, gluconate, methanesulphonate, benzenesulphonate and p-toluenesulphonate salts. Compounds of the formula (I) can also provide pharmaceutically acceptable metal salts, in particular alkali metal salts, with bases. Examples include the sodium and potassium salts.

A preferred group of compounds of formula (I) is that wherein R^1 is H, methyl or ethyl; R^2 is C_1-C_3 alkyl; R^3 is C_2-C_3 alkyl; R^4 is C_1-C_2 alkyl optionally substituted with OH, NR^5R^6, $CONR^5R^6$ or CO_2R^7; acetyl optionally substituted with NR^5R^6; hydroxyethyl substituted with NR^5R^6; ethoxymethyl optionally substituted with OH or NR^5R^6; CH=CHCN; $CH=CHCONR^5R^6$; $CH=CHCO_2R^7$; CO_2H; $CONR^5R^6$; Br; NR^5R^6; $NHSO_2NR^5R^6$; $NHSO_2R^8$; or pyridyl or imidazolyl either of which is optionally substituted with methyl; R^5 and R^6 are each independently H, methyl or ethyl, or together with the nitrogen atom to which they are attached form a piperidino, morpholino, 4-(NR^9)-1-piperazinyl or imidazolyl group wherein said group is optionally substituted with methyl or hydroxy; R^7 is H or t-butyl; R^8 is methyl or $CH_2CH_2CH_2NR^5R^6$; and R^9 is H, methyl, benzyl, 2-hydroxyethyl or acetyl.

A particularly preferred group of compounds of formula (I) is that wherein R^1 is methyl; R^2 is n-propyl; R^3 is ethyl or n-propyl; R^4 is $CH_2NR^5R^6$, $CH_2OCH_2CH_2NR^5R^6$, $CH_2OCH_2CH_3$, $CH_2OCH_2CH_2OH$, $COCH_2NR^5R^6$, $CH(OH)CH_2NR^5R^6$, $CH=CHCON(CH_3)_2$, $CH=CHCO_2R^7$, CO_2H, $CONR^5R^6$, Br, $NHSO_2NR^5R^6$, $NHSO_2CH_2CH_2CH_2NR^5R^6$, 2-pyridyl, 1-imidazolyl or 1-methyl-2-imidazolyl; R^5 and R^6 together with the nitrogen atom to which they are attached form a piperidino, 4-hydroxypiperidino, morpholino, 4-(NR^9)-1-piperazinyl or 2-methyl-1-imidazoyl group; R^7 is H or t-butyl; and R^9 is H, methyl, benzyl, 2-hydroxyethyl or acetyl.

Especially preferred individual compounds of the invention include:

5-[2-ethoxy-5-(1-methyl-2-imidazolyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

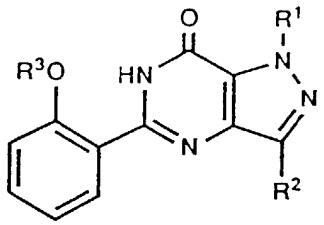
5-[2-ethoxy-5-(4-mehyl-1-piperazinylcarbonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-[5-(4-acetyl-1-piperazinyl)acetyl-2-ethoxyphenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-(2-ethoxy-5-morpholinoacetylphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one; and

5-(5-morpholinoacetyl-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3- d]pyrimidin-7-one.

Depending on the nature of R^4, the compounds of formula (I) may be prepared by a variety of methods from a compound of formula (II) :

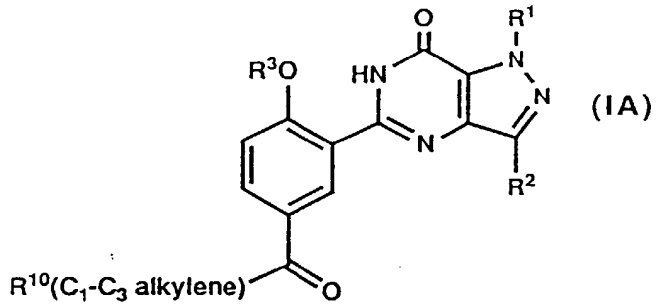


(II)

wherein R^1, R^2 and R^3 are as previously defined. For example, when R^4 is C_2-C_4 alkanoyl, the required product is obtainable by conventional Friedel-Crafts acylation whereby (II) is reacted with about a 2-fold excess of an acyl halide of formula (C_1-C_3 alkyl)COY, wherein Y is halo, preferably chloro or bromo, in the presence of about a 3-fold excess of a Lewis acid such as aluminium chloride or aluminium bromide, in a suitable solvent, e.g. dichloromethane, at from about 0°C to the reflux temperature of the reaction medium. When R^4 is C_2-C_4 alkanoyl substituted with NR^5R^6, wherein R^5 and R^6 are as previously defined, the product is obtained from (II) via the intermediacy of the corresponding haloke-

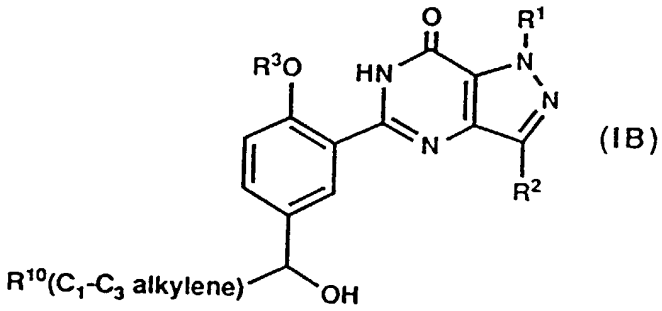
tone, i.e. a compound of formula (I) wherein R^4 is $CO(C_1\text{-}C_3$ alkylene)X and X is halo, preferably chloro or bromo, by reaction of the appropriate haloketone with the required amine of formula R^5R^6NH in the presence of at least one equivalent of base to scavenge the liberated acid by-product (HX), in a suitable solvent, e.g. acetonitrile, at about room temperature. The base may be an inorganic salt such as anhydrous potassium carbonate, a tertiary amine such as triethylamine, or excess reactant amine. In cases wherein either R^5 or R^6 is H, it may be advantageous to use a protected amine of formula R^5NHP or R^6NHP wherein P is a compatible protecting group, e.g. benzyl which can be subsequently removed by catalytic hydrogenation. When both R^5 and R^6 are H, an ammonia equivalent of formula P'_2NH, wherein P' is a protecting group such as t-butoxycarbonyl, may be beneficially employed. In this case, the potassium salt of the non-basic aminating reagent is used for reaction with the haloketone; deprotection is effected by acidolysis using, for example, hydrogen chloride, which allows convenient isolation of the desired aminoketone as its hydrochloric salt. The intermediate haloketone is also obtained via Friedel-Crafts chemistry, as described above, in this case between (II) and the appropriate haloacyl halide of formula $X(C_1\text{-}C_3$ alkylene)COY, wherein X and Y are as previously defined.

The above ketones of general formula (IA):



(IA)

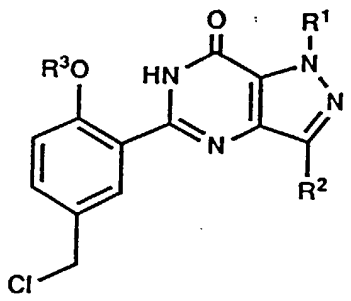
wherein R^{10} is either H or NR^5R^6, and R^1, R^2, R^3, R^5 and R^6 are as previously defined, may be reduced to provide the corresponding alcohol derivatives of general formula (IB) :



(IB)

wherein R^1, R^2, R^3 and R^{10} are as previously defined. The reducing agent is preferably sodium borohydride and the reaction may be conducted in a suitable solvent, e.g. ethanol, at about room temperature.

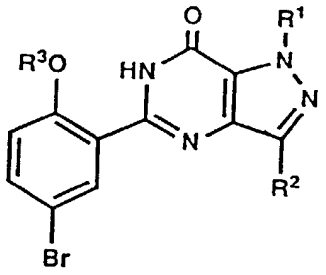
A compound of formula (I) wherein R^4 is hydroxymethyl and R^1, R^2 and R^3 are as previously defined may be prepared by subjecting a compound of formula (II) to standard chloromethylation conditions, e.g. paraformaldehyde and concentrated hydrochloric acid, at from about room temperature to about 120°C, to provide the intermediate chloromethyl derivative of formula (III), which is then treated with an alkali metal hydroxide, e.g. sodium hydroxide or potassium hydroxide, in a suitable solvent such as an ethylene glycol-dimethyl sulphoxide mixture at from about room temperature to about 100°C.



(III)

The above chloromethyl derivatives (III), wherein R^1, R^2 and R^3 are as previously defined, are valuable intermediates in the synthesis of further compounds of formula (I). For example, treatment of (III) with C_2- or C_3- alkanol in the presence of about one equivalent of an alkali metal, preferably sodium, at about room temperature, affords the corresponding C_2- or C_3-alkoxymethyl derivatives respectively. Similarly, when a C_2- or C_3-diol is employed, the analogous hydroxy (C_2- or C_3-alkoxy)methyl compounds are obtained. The latter may be further transformed by activation of the terminal hydroxy group, e.g. by conventional mesylation using about a 10% excess of mesyl chloride, in pyridine as solvent, at from about 0°C to about room temperature, followed by reaction of the mesylate with, for example, an amine of formula R^5R^6NH. Preferably the reaction is conducted with up to a 5-fold excess of amine in a suitable solvent, e.g. acetonitrile, at the reflux temperature of the reaction medium. As discussed above, when either R^5 or R^6 is H or both are H, an amine protection-deprotection strategy may be profitably employed. Thus are provided compounds of formula (I) wherein R^4 is (C_2-C_3)alkoxymethyl optionally substituted with either OH or NR^5R^6, and R^1, R^2, R^3, R^5 and R^6 are as previously defined.

The higher homologues of the above compounds, i.e. those compounds of formula (I) wherein R^4 is (C_2-C_3)alkoxyethyl optionally substituted with either OH or NR^5R^6, may be synthesised by similar procedures from the 2-chloroethyl, 2-bromoethyl or 2-mesyloxyethyl analogues of (III) which, in turn, are derivable from the corresponding 2-hydroxyethyl precursor by standard procedures. This precursor may be prepared for example from a compound of formula (I), wherein R^4 is bromo and R^1, R^2 and R^3 are as previously defined (formula (IV)), by lithium-bromine exchange using n-butyllithium, followed by reaction of the aryllithium intermediate (vide infra) with ethylene oxide.



(IV)

The chloromethyl intermediates of formula (III) may also be used for the preparation of compounds of formula (I), wherein R^4 is $CH_2NR^5R^6$ and R^1, R^2, R^3, R^5 and R^6 are as previously defined, by reaction with the appropriate amine of formula R^5R^6NH (or protected version thereof - vide supra). Preferably the reaction is carried out with about a 3-fold excess of amine in a suitable solvent, e.g. 2-butanone, at from about 0°C to the reflux temperature of the reaction medium. By analogy, compounds of formula (I) wherein R^4 is (C_2-C_4 alkylene)NR^5R^6 may be conveniently obtained from the appropriate chloro, bromo, or mesyloxy precursor which, in turn, is derivable from the corresponding alcohol (see above for a synthetic approach to the 2-hydroxyethyl analogue). The 3-hydroxypropyl and 4-hydroxybutyl analogues may be prepared by catalytic hydrogenation of the alkenols obtained when the above-mentioned bromo compound of formula (IV) is subjected to Heck reaction conditions (vide infra) with allyl alcohol or 3-buten-1-ol respectively.

The chloromethyl intermediates may further be employed to furnish the corresponding methyl derivatives, i.e. compounds of formula (I) wherein R^4 is CH_3 and R^1, R^2 and R^3 are as previously defined. This can be achieved by catalytic hydrogenation using a palladium on charcoal catalyst, in a suitable solvent such as ethyl acetate, at about 50 p.s.i. (3.45 bar) and room temperature. By analogy, when R^4 is ethyl, n-propyl or n-butyl, such compounds of formula (I) may also be obtained from the corresponding alkyl chlorides derived, in turn, from the appropriate alcohols mentioned above by standard methodology. Other alcohol derivatives, e.g. the corresponding bromide or mesylate, may also be used.

The above bromo derivatives (IV), which are valuable intermediates in the synthesis of yet further compounds of formula (I), may be prepared from a compound of formula (II) by direct bromination in a suitable solvent. This may be achieved, for example, either with about a 60% excess of N-bromosuccinimide in dimethylformamide at room temperature or with a similar excess of bromine in glacial acetic acid at from about room temperature to about 100°C. Alternatively, (IV) and the corresponding fluoro, chloro and iodo analogues may be obtained from the primary amine (vide infra) via classical sequential diazotisation-halogenation procedures including, for example, the Schiemann, Sandmeyer and Gatterman reactions.

By exploitation of Heck methodology, the bromo intermediate (IV) can be transformed to compounds of formula (I), wherein R^4 is CH=CHCN, CH=CHCONR^{5}R^6 or CH=CHCO$_2$R^7 and R^1, R^2, R^3, R^5, R^6 and R^7 are as previously defined, by employment of acrylonitrile or the appropriate acrylic acid amide or ester derivative. The reaction is generally carried out with about a 50% excess of both the alkene reagent and a tertiary amine such as triethylamine, in the presence of about 0.1 equivalents of a tertiary arylphosphine, preferably tri-o-tolylphosphine, and about 0.05 equivalents of palladium(II) acetate, in a suitable solvent such as acetonitrile, at the reflux temperature of the reaction medium. The resulting acrylic esters may be hydrolysed if desired, e.g. using aqueous sodium hydroxide solution, with methanol as co-solvent, to afford the corresponding cinnamic acids. Moreover, all the alkenyl products thus synthesised may be subjected to catalytic hydrogenation, e.g. using 5% palladium on charcoal in a suitable solvent at about 15 p.s.i. (1.0 bar) and room temperature, to provide compounds of formula (I) wherein R^4 is CH_2CH_2CN, $CH_2CH_2CONR^5R^6$ or $CH_2CH_2CO_2R^7$ and R^1, R^2, R^3, R^5, R^6 and R^7 are as previously defined for formula (I). An alternative reduction strategy, in which the acrylonitrile derivative (cinnamonitrile analogue) is exhaustively hydrogenated with Raney nickel in glacial acetic acid, affords a compound of formula (I) wherein R^4 is 3-aminopropyl and R^1, R^2 and R^3 are as previously defined.

The higher homologues, i.e. compounds of formula (I) wherein R^4 is either C_3-C_4 alkyl or C_3-C_4 alkenyl substituted with CN, CONR^{5}R^6 or CO$_2$R^7, or is 4-aminobutyl, may be derived from the previously mentioned alkenols obtained from Heck reactions between the bromo compound of formula (IV) and either allyl alcohol or 3-buten-1-ol. The conventional procedures necessary for transformation of the terminal hydroxyl group via a suitably reactive derivative, e.g. the corresponding chloride, bromide or mesylate, to the required functional groups will be well known to persons skilled in the art, and will be equally applicable to the 2-hydroxyethyl analogue (vide supra) thereby offering an alternative to Heck methodology. Compounds of formula (I), wherein R^4 is CH_2CN, $CH_2CONR^5R^6$, $CH_2CO_2R^7$ or $CH_2CH_2NH_2$, may be obtained from the chloromethyl intermediates of formula (III) by reaction with an alkali metal cyanide, e.g. sodium cyanide or potassium cyanide, followed by standard transformations or the resulting nitrile.

As a general alternative to the above Heck reaction approach, the desired alkenes (and derived alkanes via catalytic hydrogenation) may be obtained using a Wittig-Horner strategy in which an aldehyde of formula (I), wherein R^4 is CHO and R^1, R^2 and R^3 are as previously defined, is reacted with the appropriate phosphonium salt or phosphonate in the presence of a suitable base. The aldehyde itself is obtainable for formylation, e.g. using dimethylformamide, of the previously described aryllithium derivative of (IV) and, by analogy, is also a convenient precursor to compounds of formula (I) wherein R^4 is C_2-C_4 alkenyl or C_2-C_4 alkyl and R^1, R^2 and R^3 are as previously defined.

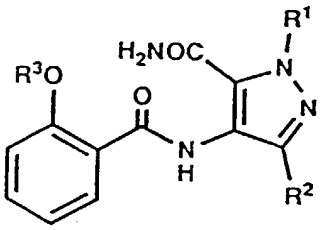
This aryllithium intermediate is also useful in the preparation of compounds of formula (I) wherein R^4 is CONR^{5}R^6 or CO$_2$R^7 and R^1, R^2, R^3, R^5, R^6 and R^7 are as previously defined. For example, lithiation of (IV) in dry tetrahydrofuran at about -78°C using about a 5-fold excess of a solution of n-butyllithium in hexane, quenching of the resulting aryllithium with carbon dioxide at about -40°C, and aqueous work-up at about 0°C including careful acidification to pH 3, furnishes the corresponding benzoic acid derivative. The acid may be activated under mild conditions, such as those obtaining in peptide bond formation via amino acid coupling procedures, and converted to an ester or amide derivative as required. For example, activation of the benzoic acid using a carbodiimide/1-hydroxybenzotriazole combination in the presence of the required amine of formula R^{5}R^{6}NH or alcohol of formula R^{7}OH, in a suitable solvent such as dichloromethane at about 0°C to room temperature, yields the corresponding amide or ester respectively.

The bromo intermediates of formula (IV) are also of utility in the synthesis of compounds of formula (I) wherein R^4 is phenyl or heterocyclyl, each of which is optionally substituted with methyl, and R^1, R^2 and R^3 are as previously defined. When R^4 is phenyl or C-linked heterocyclyl, it may be introduced via palladium-catalysed coupling of the zincate derivative generated in situ from the corresponding phenyllithium or heterocyclyllithium intermediate; the latter, in turn, may be obtained from either the heterocycle or haloheterocycle as necessary by treatment with n-butyllithium. Thus, for example, the phenyllithium or heterocyclyllithium (in the presence of about 1 extra equivalent of n-butyllithium to accommodate the active hydrogen atom of the pyrazolopyrimidinone substrate) is treated with about 2 equivalents of anhydrous zinc chloride in dry tetrahydrofuran at about -78°C followed, at about room temperature, by (IV) and the palladium catalyst, preferably tetrakis(triphenylphosphine)palladium(0). The reaction mixture can be heated to reflux with addition of up to about 2 further equivalents of anhydrous zinc chloride if necessary. When R^4 is N-linked heterocyclyl, the reaction may be conducted with up to about a 5-fold excess of the appropriate heterocycle in the presence of about a 10% excess of base, e.g. anhydrous potassium carbonate, to scavenge the hydrogen bromide by-product, together with about a 10% excess of copper-bronze and about 0.25 equivalents of iodine catalyst in a suitable solvent, e.g. dimethylformamide, at about the reflux temperature of the reaction medium.

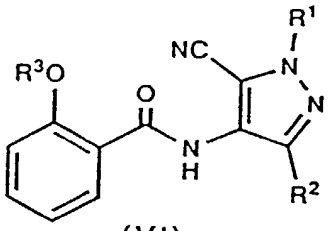
Compounds of formula (I), wherein R^4 is $NHSO_2NR^5R^6$ or $NHSO_2R^8$ and R^1, R^2, R^3, R^5, R^6 and R^8 are as previously defined, may be synthesised from the corresponding primary amine which, in turn, is obtained by nitration of (II) using, e.g. a conventional concentrated nitric acid/concentrated sulphuric acid combination, followed by reduction of the nitroarene by catalytic hydrogenation using conventional procedures. The reaction is generally carried out using equimolar quantities of the primary amine of formula (I), wherein R^4 is NH_2 and R^1, R^2 and R^3 are as previously defined, and either the required sulphamoyl halide or alkylsulphonyl halide (preferably the chlorides) of formula $R^5R^6NSO_2$halo or R^8SO_2halo respectively, in the presence of excess tertiary amine such as triethylamine or pyridine to scavenge the acid by-product, in a suitable solvent, e.g. dichloromethane, at from about 0°C to about room temperature. Pyridine may conveniently function as both base and solvent when desired, and the reaction may be optionally catalysed by the addition of about 0.1 to 0.2 equivalents of a 4-t-aminopyridine such as 4-dimethylaminopyridine. When both R^5 and R^6 are H, the desired product may also be obtained by reaction of the primary amine with sulphamide in a suitable solvent, e.g. 1,4-dioxan, at about 100°C.

When, in transformations of compounds of formula (II) to compounds of formula (I), R^3 is a group susceptible to reaction or removal under the particular conditions employed to introduce R^4, said R^3 group may itself be introduced at the final stage of the synthesis. Thus a phenol of formula (II), wherein R^3 is H, and R^1 and R^2 are as previously defined, which is obtainable for example by Pd°-mediated deprotection of the O-allyl analogue, i.e. a compound of formula (II) wherein R^3 is allyl, and R^1 and R^2 are as previously defined, serves as the substrate for the subsequent reactions involved in introducing the various R^4 substituents. A final O-alkylation of the phenolic group is then necessary to furnish a compound of formula (I), wherein R^1, R^2, R^3 and R^4 are as previously defined. This may be achieved under standard conditions using the appropriate alkyl chloride, bromide or sulphonate in the presence of a base such as anhydrous potassium carbonate, in a suitable solvent, e.g. 2-butanone, at the reflux temperature of the reaction mixture. Alternatively, the alkylation may be effected under typical Mitsunobu reaction conditions.

A compound of formula (II) may be prepared from a compound of formula (V):



(V)

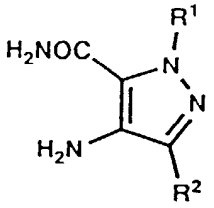


(VI)

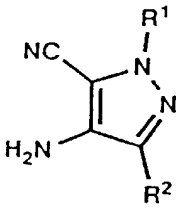
wherein R^1, R^2 and R^3 are as previously defined, by the application of known cyclisation methods for pyrimidinone ring formation. Thus, for example, the cyclisation may be effected by the treatment of (V) with a base such as sodium hydroxide or potassium carbonate, optionally in the presence of hydrogen peroxide, in an ethanol-water medium at reflux temperature. Under these conditions the related nitrile of formula (VI), wherein R^1, R^2 and R^3 are as previously defined, may also be employed as the precursor to (IV).

In an alternative cyclisation procedure, compounds of the formula (II) may be obtained by treatment of (V) with polyphosphoric acid at about 140°C.

Compounds of formulae (V) and (VI) may be prepared from compounds of formulae (VII) and (VIII) respectively:

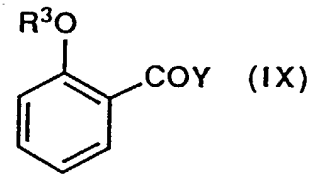


(VII)



(VIII)

wherein R^1 and R^2 are as previously defined, by reaction with a compound of formula (IX):

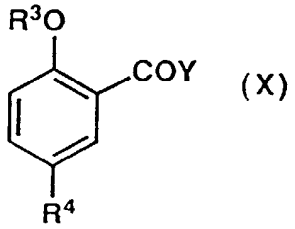


(IX)

wherein R^3 and Y are as previously defined.

The reaction is generally carried out using an excess of (IX) in the presence of an excess of a tertiary amine such as triethylamine to act as scavenger for the acid by-product (HY), optionally in the presence of a catalyst such as 4-dimethylaminopyridine, in an inert solvent such as dichloromethane at from about 0°C to room temperature.

Compounds of formula (I) may be obtained more directly from a compound of formula (X):



(X)

wherein R^3, R^4 and Y are as previously defined, when such acyl halides are readily accessible, by reaction with either (VII) or (VIII) and subsequent ring-closure of the product as described above. Clearly this alternative synthetic route will only be appropriate when R^4 is compatible with the reaction conditions obtaining in both steps, e.g. when R^4 is acetyl as illustrated by Example 17.

The aminopyrazoles of formulae (VII) and (VIII), the acyl halides of formulae (IX) and (X), and the intermediates employed for introduction of the various R^4 substituents into compounds of formula (II) to afford compounds of formula (I), when neither commercially available nor subsequently described, can be obtained by conventional synthetic procedures, in accordance with literature precedent, from readily accessible starting materials using appropriate reagents and reaction conditions.

Certain of the compounds of formula (I), wherein R^9 is as previously defined but not hydrogen, may be prepared directly from the corresponding 4-N-unsubstituted piperazine analogue, that is the precursor wherein R^9 is hydrogen, using appropriate standard synthetic procedures.

All of the above reactions are entirely conventional and the necessary reagents and conditions for their performance can readily be established by reference to standard text books and to the Examples provided hereafter. Alternatives and variations will also be evident to persons skilled in the art to enable all the compounds defined by formula (I) to be prepared.

The biological activities of the compounds of the present invention were determined by the following test methods.

Phosphodiesterase activity

Compound affinities for cGMP and cAMP PDEs are assessed by determination of their IC_{50} values (the concentration of inhibitor required for 50% inhibition of enzyme activity). The PDE enzymes are isolated from rabbit platelets and rat kidney, essentially by the method of W.J. Thompson et al. (Biochem., 1971, 10, 311). The calcium/calmodulin (Ca/CAM)-independent cGMP PDE and the cGMP-inhibited cAMP PDE enzymes are obtained from rabbit platelets whilst, of the four major PDE enzymes of the rat kidney, the Ca/CAM-dependent cGMP PDE (fraction I) is isolated. Assays are performed using a modification of the "batch" method of W.J. Thompson and M.M. Appleman (Biochem., 1979, 18, 5228). Results from these tests show that the compounds of the present invention are potent and selective inhibitors of both cGMP PDEs.

Platelet anti-aggregatory activity

This is assessed by the determination of a compound's ability to inhibit platelet aggregation in vitro induced by

platelet activating factor (PAF), and to potentiate the platelet antiaggregatory action in vitro of activators of guanylate cyclase such as nitroprusside and EDRF. Washed platelets are prepared essentially by the method of J.F. Mustard et al. (Methods in Enzymol., 1989, 169, 3) and aggregation is determined using standard turbidimetric techniques as described by G.V.R. Born, (J. Physiol. (Lond), 1962, 162, 67P).

Antihypertensive activity

This is assessed following intravenous or oral administration of a compound to spontaneously hypertensive rats. Blood pressure is recorded via a cannula implanted in the carotid artery of either conscious or anaesthetised animals.

For administration to man in the curative or prophylactic treatment of angina, hypertension or congestive heart failure, oral dosages of the compounds will generally be in the range of from 4-800 mg daily for an average adult patient (70 kg). Thus for a typical adult patient, individual tablets or capsules contain from 2-400 mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier, for administration in single or multiple doses, once or several times per day. Dosages for intravenous, buccal or sublingual administration will typically be within the range of from 1-400 mg per single dose as required. In practice the physician will determine the actual dosing regimen which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case but there can be individual instances in which higher or lower dosage ranges may be merited, and such are within the scope of this invention.

For human use, the compounds of formula (I) can be administered alone, but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they may be administered orally, buccally or sublingually, in the form of tablets containing excipients such as starch or lactose, or in capsules or ovules either alone or in admixtures with excipients, or in the form of elixirs or suspensions containing flavouring or colouring agents. The compounds may also be injected parenterally, for example intravenously, intramuscularly, subcutaneously or intracoronarily. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other substances, for example salts, or monosaccharides such as mannitol or glucose, to make the solution isotonic with blood.

Thus the invention provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier.

The invention also provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for use in medicine.

The invention further provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the treatment of stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, stroke, peripheral vascular disease, conditions of reduced blood vessel patency e.g. post-PTCA, chronic asthma, bronchitis, allergic asthma, allergic rhinitis, glaucoma, or diseases characterised by disorders of gut motility, e.g. IBS.

In a further aspect, the invention provides a method of treating or preventing stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, stroke, peripheral vascular disease, conditions of reduced blood vessel patency e.g. post-PTCA, chronic asthma, bronchitis, allergic asthma, allergic rhinitis, glaucoma, or diseases characterised by disorders of gut motility, e.g. IBS, in a mammal (including a human being), which comprises administering to said mammal a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity.

The syntheses of the compounds of the invention and of the intermediates for use therein are illustrated by the following Examples and Preparations. The purity of the compounds was routinely monitored by thin layer chromatography (TLC) using Merck Kieselgel 60 F_{254} plates. ^{1}H-Nuclear magnetic resonance spectra were recorded using either a Nicolet QE-300 or a Bruker AC-300 spectrometer and were in all cases consistent with the proposed structures.

EXAMPLE 1

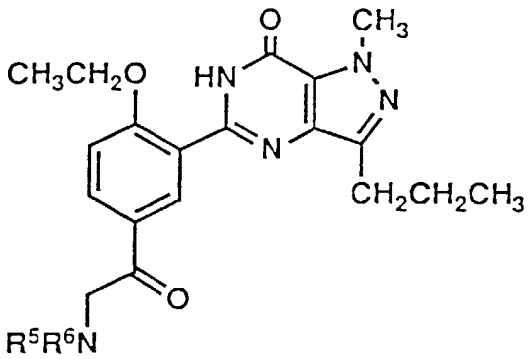
5-(2-Ethoxy-5-piperidinoacetylphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

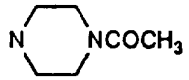
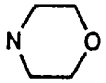
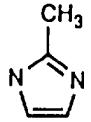
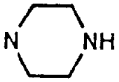
Piperidine (0.22 ml, 0.0022 mol) was added to a stirred suspension of 5-(5-bromoacetyl-2-ethoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (Preparation 8, 0.95 g, 0.0022 mol) and anhydrous potassium carbonate (0.6 g, 0.0044 mol) in acetonitrile (50 ml) at room temperature. After 18 hours the mixture was evaporated under vacuum, the residue dissolved in water (50 ml) and the solution extracted with ethyl acetate (3 x 30 ml). The organic extracts were combined, washed with brine (3 x 20 ml), dried (Na_2SO_4) and evaporated under vacuum. The resulting yellow solid was chromatographed on silica gel (12 g), using a methanol in dichloromethane elution gradient (0-2% methanol), to give an off-white solid. Crystallisation from ethyl acetate-hexane gave the title compound

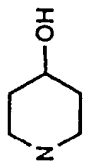
as an off-white powder (0.27 g, 28%), m.p. 149-151°C. Found: C,66.13; H,6.90; N,15.95. $C_{24}H_{31}N_5O_3$ requires C, 65.88; H,7.14; N,16.01%.

EXAMPLES 2-8

The following Examples were prepared by the procedure of Example 1 using the appropriate amine.



Example	NR^5R^6	% yield	m.p. (°C)	Analysis % (theoretical in brackets) C	H	N
2	$N(CH_2CH_3)_2$	4	120-121	65.21 (64.92	7.31 7.34	16.37 16.46)
3		23	183-185	62.48 (62.48	6.62 6.71	17.32 17.49)
4		29	159-160	63.20 (62.85	6.58 6.65	15.87 15.94)
5		21	202-204	61.84 (62.28	6.12 6.14	18.68 18.95)a
6		39	142-143	62.83 (63.00	7.09 6.90	18.90 19.16)

Example	NR^5R^6	% yield	m.p. (°C)	Analysis % (theoretical in brackets) C	H	N
7		36	135-136	62.46 (62.22	6.91 7.10	17.36 17.41)
8		40	151-152	63.64 (63.56	6.80 6.89	15.63 15.44)

a 0.50 H_2O

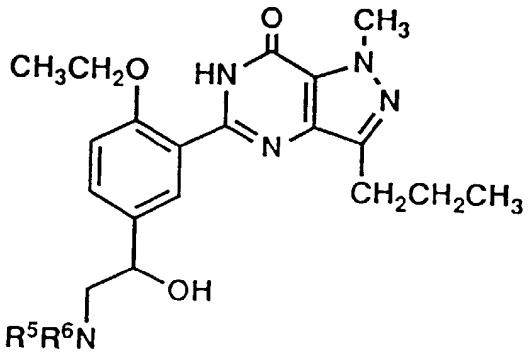
EXAMPLE 9

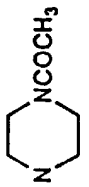
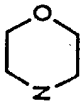
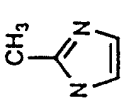
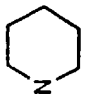
5-{2-Ethoxy-5-[1-hydro-2-(1-piperazinyl)ethyl]phenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Sodium borohydride (0.01 g, 0.0027 mol) was added to a stirred suspension of 5-[2-ethoxy-5-(1-piperazinylacetyl) phenyl]-1-methyl-3-n-propyl-1, 6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (0.12 g, 0.0027 mol) in ethanol (10 ml) and the resulting solution stirred at room temperature for 18 hours. The solvent was removed by evaporation under vacuum, the residue suspended in saturated aqueous sodium carbonate solution (50 ml) and this mixture extracted with dichloromethane (3 x 20 ml). The organic extracts were combined, dried (Na_2SO_4) and evaporated under vacuum to give an oil. Trituration with ether gave a white solid, crystallisation of which from ethyl acetate-hexane gave the title compound as a white powder (0.050 g, 42%), m.p. 139-140°C. Found: C,62.55; H,7.44; N,18.79. $C_{23}H_{32}N_6O_3$ requires C,62.71; H,7.32; N,19.08%.

EXAMPLES 10-13

The following Examples were prepared by the procedure of Example 9 using the appropriate ketones (Examples 3, 4, 5 and 1 respectively).



Example	NR^5R^6	% yield	m.p. (°C)	Analysis % (theoretical in brackets) C	H	N
10		37	139-141	61.92 (62.22	7.01 7.10	17.08 17.42)
11		69	125-127	62.23 (62.56	7.10 7.08	15.53 15.86)
12		77	221-222	63.68 (63.29	6.39 6.47	19.17 19.25)
13		97	117-118	65.51 (65.58	7.57 7.57	15.84 15.93)

EXAMPLE 14

1-Methyl-5-(5-morpholinoacetyl-2-n-propoxyphenyl)-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

This compound was prepared from morpholine and 5-(5-bromoacetyl-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimdin-7-one (Preparation 11), following the procedure of Example 1, and was obtained as white crystals (47%), m.p. 128-129°C. Found: C,63.62; H,7.07; N,15.53. $C_{24}H_{31}N_5O_4$ requires C,63.56; H, 6.89; N,15.44%.

EXAMPLE 15

1-Methyl-5-[5-(4-methyl-1-piperazinylacetyl)-2-n-propoxyphenyl]-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

This compound was prepared from 4-methylpiperazine and 5-(5-bromoacetyl-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (Preparation 11), following the procedure of Example 1, and was obtained as a white solid (27%), m.p. 124-125°C. Found: C,63.96; H,7.19; N,17.80. $C_{25}H_{34}N_6O_3$ requires C,64.36; H, 7.34; N,18.01%.

EXAMPLE 16

5-[5-(1-Hydroxy-2-morpholinoethyl)-2-n-propoxyphenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d] pyrimidin-7-one

This compound was prepared from 1-methyl-5-(5-morpholinoacetyl-2-n-propoxyphenyl)-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, following the procedure of Example 9, and was obtained as a white solid (28%), m.p. 104-105°C. Found: C,62.90; H,7.50; N,15.48. $C_{24}H_{33}N_5O_4$ requires C,63.28; H,7.30; N,15.37%.

EXAMPLE 17

5-(5-Acetyl-2-ethoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

The title compound was prepared from 4-(5-acetyl-2-ethoxybenzamido)-1-methyl-3-n-propylpyrazole-5-carboxamide (Preparation 15), following the procedure of Preparation 7, and was obtained as a white solid (77%), m.p. 196-198°C. Found: C,64.35; H,6.16; N,15.85. $C_{19}H_{22}N_4O_3$ requires C,64.39; H,6.26; N,15.81%.

EXAMPLE 18

5-(5-Bromo-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

N-Bromosuccinimide (2.6 g, 0.016 mol) in dimethylformamide (40 ml) was added dropwise to a stirred solution of 5-(2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (Preparation 10, 4.0 g, 0.010 mol) in dimethylformamide (40 ml) at room temperature. After 7 hours the solvent was removed by evaporation under vacuum, the residue suspended in saturated aqueous sodium carbonate solution, and the resulting solution extracted with ethyl acetate (3 x 50 ml). The organic extracts were combined, dried (Na_2SO_4) and evaporated under vacuum. Trituration of the residue with ether, followed by crystallisation from ethyl acetate-hexane, gave the title compound as white crystals (3.39 g, 68%), m.p. 117-118°C. Found: C,53.15; H,5.03; N,13.78. $C_{18}H_{21}BrN_4O_2$ requires C, 53.34; H,5.22; N,13.82%.

EXAMPLE 19

(E)-3-(1-Methyl-7-oxo-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-n-propoxycinnamic acid t-butyl ester

To a solution of 5-(5-bromo-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (1.0 g, 0.0025 mol) and triethylamine (0.38 g, 0.0038 mol) in acetonitrile (2 ml), was added palladium(II) acetate (0.03 g, 0.00013 mol), tri-o-tolylphosphine(0.076 g, 0.00025 mol) and t-butyl acrylate (0.48 g, 0.0038 mol). The mixture was heated under reflux for 4 hours, then cooled and evaporated under vacuum. The residue was suspended in water

(30 ml) and extraction with dichloromethane (3 x 20 ml) effected. The organic extracts were combined, dried (Na_2SO_4) and evaporated under vacuum to give a yellow-green solid. Chromatography on silica gel (12 g), using a methanol in dichloromethane elution gradient (0-2% methanol), followed by crystallisation from ethyl acetate-hexane gave the title compound as a white solid (0.65 g, 58%), m.p. 167-168°C. Found: C,66.47; H,7.00; N,12.31. $C_{25}H_{32}N_4O_4$ requires C, 66.35; H,7.13; N,12.38%.

EXAMPLE 20

(E)-3-(1-Methyl-7-oxo-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]-pyrimidin-5-yl)-4-n-propoxycinnamic acid

2N Aqueous sodium hydroxide solution (2.28 ml, 0.0046 mol) was added to a solution of (E)-3-(1-methyl-7-oxo-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-n-propoxycinnamic acid t-butyl ester (0.40 g, 0.00088 mol) in methanol (2.3 ml) and the mixture was heated under reflux for 18 hours. The methanol was removed by evaporation under vacuum, the residue dissolved in water (25 ml), and the solution extracted with ethyl acetate (4 x 15 ml). The aqueous layer was separated, acidified to pH 1 with hydrochloric acid, and then extracted with a mixture of methanol and ethyl acetate (3:97, 4 x 20 ml). The organic extracts were combined, dried (Na_2SO_4) and evaporated under vacuum, then the residue crystallised from ethyl acetate to give the title compound as a white solid (0.27 g, 77%), m.p. 229-230°C. Found: C,63.64; H,5.98; N,14.14. $C_{21}H_{24}N_4O_4$ requires C,63.46; H,6.34; N,14.10%.

EXAMPLE 21

5-(5-Bromo-2-ethoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Bromine (0.93 g, 0.0058 mol) was added dropwise to a stirred solution of 5-(2-ethoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (Preparation 7, 1.1 g, 0.00352 mol) in glacial acetic acid (20 ml). The mixture was stirred at 100°C for 6.5 hours and the solvent was then removed by evaporation under vacuum. The residue was dissolved in a 9:1 mixture of methanol in dichloromethane (50 ml), and the solution washed with saturated aqueous sodium bicarbonate solution (50 ml), water (50 ml) and saturated brine (50 ml), then dried ($MgSO_4$) and evaporated under vacuum. The residue was chromatographed on silica gel (15 g) eluting with a mixture of methanol and dichloromethane (1:99) to give, after crystallisation from acetonitrile, the title compound (0.62 g, 45%), m.p. 157-159°C. Found: C,52.41; H,5.25; N,14.01. $C_{17}H_{19}BrN_4O_2$ requires C,52.18; H,4.89; N,14.32%.

EXAMPLE 22

(E)-4-Ethoxy-3-(1-methyl-7-oxo-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-5-yl)cinnamic acid t-butyl ester

The title compound was prepared from 5-(5-bromo-2-ethoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo [4,3-d]pyrimidin-7-one following the procedure of Example 19 and was obtained as a white crystalline solid (31%), m. p. 179-180°C. Found: C,65.83; H,6.90; N,12.75. $C_{24}H_{30}N_40_4$ requires C,65.89; H,6.68; N,12.81%.

EXAMPLE 23

(E)-4-Ethoxy-3-(1-methyl-7-oxo-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-5-yl)cinnamic acid

The title compound was prepared from (E)-4-ethoxy-3-(1-methyl-7-oxo-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d] pyrimidin-5-yl)cinnamic acid t-butyl ester following the procedure of Example 20 and was obtained as white crystals (66%), m.p. 234-236°C. Found: C,63.01; H,5.59; N,14.62. $C_{20}H_{22}N_4O_4$ requires C,62.82; H,5.80; N,14.65%.

EXAMPLE 24

3-[4-Ethoxy-3-(1-methyl-7-oxo-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl]propanoic acid

A solution of (E)-4-Ethoxy-3-(1-methyl-7-oxo-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-5-yl)cinnamic acid (0.426 g, 0.0011 mol) in a mixture of methanol (28.5 ml), ethyl acetate (100 ml) and water (1.5 ml), was stirred with 5% palladium on charcoal catalyst (0.05 g) under a hydrogen atmosphere at room temperature and pressure for 3 hours. The catalyst was removed by filtration and the solvent removed by evaporation under vacuum. Crystallisation of the residue from ethyl acetate-hexane gave the title compound as beige crystals (0.23 g, 54%), m.p. 165-167°C. Found: C,62.24; H,6.17; N,14.09. $C_{20}H_{24}N_40_4$ requires C,62.39; H,6.33; N,14.41%

EXAMPLE 25

(E)-4-Ethoxy-3-(1-methyl-7-oxo-3-n-propyl-1,6-dihydro-7H-pyrazolo-[4,3-d]pyrimidin-5-yl)cinnamic acid dimethylamide

The title compound was prepared from N,N-dimethylacrylamide and 5-(5-bromo-2-ethoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one following the procedure of Example 19 and was obtained, following crystallisation from ethyl acetate-hexane, as colourless crystals (38%), m.p. 219-221°C. Found: C,64.15; H, 6.46; N,16.96. $C_{22}H_{27}N_5O_3$ requires C,64.53; H,6.65; N,17.10%.

EXAMPLE 26

3-[4-Ethoxy-3-(1-methyl-7-oxo-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-5-yl)phenyl]propanoic acid dimethylamide

The title compound was prepared from (E)-4-ethoxy-3-(1-methyl-7-oxo-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d] pyrimidin-5-yl)cinnamic acid dimethylamide following the procedure of Example 24 and, after crystallisation from ethyl acetate-hexane, was obtained as colourless crystals (74%), m.p. 155-157°C. Found: C,64.09; H,7.04; N,16.71. $C_{22}H_{29}N_5O_3$ requires C,64.21; H,7.10; N,17.02%.

EXAMPLE 27

(E)-4-Ethoxy-3-(1-methyl-7-oxo-3-n-propyl-1,6-dihydro-7H-pyrazolo-4,3-d]pyrimidin-5-yl)cinnamonitrile

The title compound was prepared from acrylonitrile and 5-(5-bromo-2-ethoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo-[4,3-d]pyrimidin-7-one following the procedure of Example 19 and was obtained as off-white crystals (33%). Found: C,65.99; H,5.52; N,19.07. $C_{20}H_{21}N_5O_2$ requires C,66.10; H,5.82; N,19.27%.

EXAMPLE 28

5-[5-(3-Aminopropyl)-2-ethoxyphenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

A solution of (E)-4-ethoxy-3-(1-methyl-7-oxo-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin- 5-yl)cinnamonitrile (0.25 g, 0.00064 mol) in glacial acetic acid (25 ml) was stirred with Raney nickel catalyst (25 mg) under hydrogen at room temperature and at 50 p.s.i. for 3 hours. The resulting mixture was filtered and the filtrate evaporated under vacuum. The residue was partitioned between saturated aqueous sodium carbonate solution (50 ml) and dichloromethane (30 ml), the layers separated and the aqueous phase further extracted with dichloromethane (2 x 30 ml). The organic solutions were combined, dried (Na_2SO_4) and evaporated under vacuum to give a brown solid, crystallisation of which from hexane-ethyl acetate gave the title compound as fawn crystals (96 mg, 38%), m.p. 115-117°C. Found C,65.29; H,7.35; N,18.66. $C_{20}H_{27}N_5O_2$ requires C,65.02; H,7.37; N,18.96%.

EXAMPLE 29

4-Ethoxy-3-(1-methyl-7-oxo-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-5-yl)benzoic acid

n-Butyllithium (2.5 M solution in hexane, 1.53 ml, 0.0038 mol) was added dropwise to a stirred solution of 5-(5-bromo-2-ethoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (0.60 g, 0.00074 mol) in dry tetrahydrofuran (25 ml) at -78°C under a dry nitrogen atmosphere. After 0.3 hour at -78°C, the solution was allowed to warm to -40°C and carbon dioxide gas was bubbled through the solution. The resulting solution was allowed to warm to room temperature and then poured into water; acidification to pH 3 with 2N hydrochloric acid and extraction with a 9:1 mixture of dichloromethane and methanol (4 x 50 ml) were then effected. The organic extracts were combined, dried ($MgSO_4$) and evaporated under vacuum to give a colourless solid. Chromatography of this solid on silica gel (20 g), using a methanol in dichloromethane elution gradient (2-5% methanol), gave a solid which was dissolved in a 9:1 mixture of dichloromethane and methanol (50 ml); this solution was then washed with saturated aqueous sodium carbonate solution (50 ml), dried ($MgSO_4$) and evaporated under vacuum to give the title compound as a white powder (0.144 g, 26%), m.p. 285-288°C. Found: C,60.74; H,5.72; N,15.61. $C_{18}H_{20}N_4O_4$ requires C,60.66; H,5.66; N,15.72%.

EXAMPLE 30

5-[2-Ethoxy-5-(4-methylpiperazinylcarbonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

A solution of 4-ethoxy-3-(1-methyl-7-oxo-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-5-yl)benzoic acid (0.095 g, 0.00027 mol), 1-methylpiperazine (0.265 g, 0.00265 mol), 1-(3-dimethylaminopropyl)3-ethylcarbodiimide hydrochloride (0.077 g, 0.0004 mol) and 1-hydroxybenzotriazole (0.054 g, 0.0004 mol) in dichloromethane (25 ml) was stirred at room temperature for 18 hours. The reaction solution was washed with water (25 ml), dried ($MgSO_4$) and evaporated under vacuum, and then the resulting residue crystallised from ethyl acetate-hexane to give the title compound as colourless crystals (0.03 g, 25%), m.p. 196-197°C. Found: C,63.12; H,6.81; N,18.96. $C_{23}H_{30}N_6O_3$ requires C,62.99; H,6.90; N,19.16%.

EXAMPLE 31

5-[2-Ethoxy-5-(1-imidazolyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

A solution of 5-(5-bromo-2-ethoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (0.20 g, 0.00051 mol), imidazole (0.172 g, 0.0025 mol), anhydrous potassium carbonate (0.077 g, 0.00056 mol), copper bronze (0.036 g, 0.00057 mol) and iodine (0.015 g, 0.00012 mol) in dimethylformamide (10 ml) was heated under reflux under nitrogen for 4.5 hours, cooled and poured into water (50 ml). This mixture was extracted with a 9:1 mixture of dichloromethane and methanol (6 x 50 ml) and the extracts combined, dried ($MgSO_4$) and evaporated under vacuum to give a pale brown oil. The oil was chromatographed on silica gel (20 g), eluting with a mixture of dichloromethane, methanol and triethylamine (97.8:2:0.2), to give a yellow solid, crystallisation of which from ethyl acetate-hexane gave the title compound as a cream solid (0.073 g, 38%), m.p. 193-194°C. Found: C,63.61; H,5.97; N,22.03. $C_{20}H_{22}N_6O_2$ requires C,63.48; H,5.86; N,22.21%.

EXAMPLE 32

5-[2-Ethoxy-5-(1-methyl-2-imidazolyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

n-Butyllithium (1.6 M solution in hexane, 9.6 ml, 0.0153 mol) was added to a stirred solution of 1-methylimidazole (0.628 g, 0.0077 mol) in dry tetrahydrofuran (10 ml) at -78°C, and the resulting solution stirred for 0.25 hours. A solution of anhydrous zinc chloride (2.08 g, 0.0153 mol) in dry tetrahydrofuran (15 ml) was added, the mixture allowed to warm to room temperature, then 5-(5-bromo-2-ethoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (1.0 g, 0.0026 mol) and tetrakis(triphenylphosphine)palladium(0) (0.036 g, 0.031 mol) were added and the mixture heated under reflux for 18 hours. A further quantity of anhydrous zinc chloride (2.08 g, 0.0153 mol) was added and the resulting mixture heated under reflux for a further 60 hours, then cooled; methanol (2 ml) was added and the solvent removed by evaporation under vacuum. The residue was heated with a solution of disodium ethylenediaminetetraacetic acid dihydrate (23.0 g, 0.0618 mol) in water (100 ml) to 100°C for 0.2 hour, then the resulting solution basified to pH 8 with saturated aqueous sodium carbonate solution and extracted with dichloromethane (6 x 100 ml). The organic extracts were combined, dried (Na_2SO_4) and evaporated under vacuum to give a yellow solid, purification of which by chromatography on silica gel (13 g), using a methanol-dichloromethane elution gradient (0-3% methanol), followed by crystallisation from ethyl acetate, gave the title compound as an off-white solid (0.542 g, 53%), m.p. 199-202°C. Found: C,64.45; H,6.27; N,21.56. $C_{21}H_{24}N_6O_2$ requires C,64.27; H,6.16; N,21.42%.

EXAMPLE 33

5-[2-Ethoxy-5-(2-pyridyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

The title compound was prepared from 2-bromopyridine and 5-(5-bromo-2-ethoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, following the procedure described in Example 32, and was obtained as an off-white solid (33%), m.p. 216-218°C. Found: C,67.61; H,5.81; N,17.63. $C_{22}H_{23}N_5O_2$ requires C,67.85; H,5.95; N,17.98%.

EXAMPLE 34

1-Methyl-5-(5-morpholinomethyl-2-n-propoxyphenyl)-3-n-propyl-1,6-dihydro-7H-pyrazolo-[4,3-d]pyrimidin-7-one

A solution of 5-(5-chloromethyl-2-n-propoxymethyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3- d]pyrimidin-7-one (Preparation 16, 0.60 g, 0.0016 mol) in 2-butanone (10 ml) was added dropwise to a stirred solution of morpholine (0.42 g, 0.0048 mol) in 2-butanone (40 ml) at 0°C. The solution was then heated under reflux for 16 hours, cooled and evaporated under vacuum. The residue was suspended in water (50 ml) and the suspension extracted with ethyl acetate (3 x 20 ml). The organic extracts were combined, washed with brine (2 x 30 ml), dried (Na_2SO_4) and evaporated under vacuum. The residue was chromatographed on silica gel (12 g), using an elution gradient of methanol in dichloromethane (0-2% methanol), to give an oil which solidified on trituration with hexane. Crystallisation from ethyl acetate-hexane gave the title compound as a colourless solid (0.36 g, 53%), m.p. 106-107°C. Found: C,64.76; H,7.34; N,16.36. $C_{23}H_{31}N_5O_3$ requires C,64.92; H,7.34; N,16.46%.

EXAMPLE 35

1-Methyl-5-[5-(4-methyl-1-piperazinylmethyl)-2-n-propoxyphenyl)-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d] pyrimidin-7-one

The title compound was prepared from 5-(5-chloromethyl-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one and 1-methylpiperazine, following the procedure of Example 34, and was obtained as a colourless solid (36%), m.p. 149-150°C. Found: C,65.68; H,7.83; N,19.10. $C_{24}H_{34}N_6O_2$ requires C,65.73; H,7.81; N,19.16%.

EXAMPLE 36

1-Methyl-5-(5-methyl-2-n-propoxyphenyl)-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

A solution of 5-(5-chloromethyl-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3- d]pyrimidin-7-one (0.5 g, 0.0013 mol) in ethyl acetate (50 ml) was stirred with 10% palladium on charcoal catalyst under a hydrogen atmosphere at 50 p.s.i. and room temperature. After 1 hour, the mixture was filtered and the filtrate evaporated under vacuum to give a pale green solid. Chromatography on silica gel (4 g) using a methanol in dichloromethane elution gradient gave a white solid, crystallisation of which from hexane-ethyl acetate gave the title compound as colourless needles (0.12 g, 26%), m.p. 115-116°C. Found: C,66.66; H,7.12; N,16.55. $C_{19}H_{24}N_4O_2$ requires C,67.04; H,7.11; N,16.46%.

EXAMPLE 37

5-(5-Hydroxymethyl-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

To a solution of 5-(5-chloromethyl-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (0.5 g, 0.0013 mol) in dimethyl sulphoxide (10 ml) was added sodium hydroxide (0.26 g, 0.0065 mol) and ethylene glycol (0.41 g, 0.0065 mol). The reaction mixture was heated at 100°C for 6 hours, allowed to cool and poured into water (50 ml), then the aqueous mixture extracted with ethyl acetate (3 x 30 ml). The combined extracts were filtered, dried (Na_2SO_4) and evaporated under vacuum to provide an oil which was purified by chromatography on silica gel (6 g), using a methanol in dichloromethane elution gradient (0-3% methanol). The solid product was crystallised from hexane-ethyl acetate to afford the title compound as a white solid (2%), m.p. 174-175°C. Found: C,63.97; H,6.66; N,15.57. $C_{19}H_{24}N_4O_3$ requires C,64.03; H,6.79; N,15.72%.

EXAMPLE 38

5-(5-Ethoxymethyl-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Sodium (0.15 g, 0.0013 mol) was added portionwise to ethanol (40 ml) over 1 hour. 5-(5-Chloromethyl-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3- d]pyrimidin-7-one (0.5 g, 0.0013 mol) was then added to the solution and, after 3 days at room temperature, the solvent was removed by evaporation under vacuum. The residual solid was suspended in water (50 ml) and the suspension extracted with ethyl acetate (3 x 30 ml). The extracts were then combined, dried (Na_2SO_4) and evaporated under vacuum to give a green solid. Chromatography on silica

gel (6 g) using a methanol in dichloromethane elution gradient gave, after crystallisation of the required product from a hexane-ethyl acetate mixture, the title compound as a white solid (0.2 g, 39%) m.p. 89-90°C. Found: C,65.87; H, 7.57; N,14.66. $C_{21}H_{28}N_4O_3$ requires C,65.60; H,7.34; N,14.57%.

EXAMPLE 39

5-[5-(2-Hydroxyethoxymethyl)-2-n-propoxyphenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

This compound was prepared from 5-(5-chloromethyl-2-n-propoxy-phenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one and ethylene glycol following the procedure of Example 38 and was obtained as a white solid (45%), m.p. 101-102°C. Found: C,63.13; H,6.88; N,13.98. $C_{21}H_{28}N_4O_4$ requires C,62.98; H,7.05; N,13.99%.

EXAMPLE 40

1-Methyl-5-[5-(2-morpholinoethoxymethyl)-2-n-propoxyphenyl]-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

(a) Methanesulphonyl chloride (0.56 g, 0.0049 mol) was added to a stirred solution of 5-[5-(2-hydroxyethoxymethyl)-2-n-propoxyphenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (1.8 g, 0.0045 mol) in pyridine (25 ml) at 0°C. After 18 hours at room temperature, the solvent was removed by evaporation under vacuum and the residue partitioned between 2N hydrochloric acid (30 ml) and dichloromethane (30 ml). The aqueous layer was separated and extracted with dichloromethane (2 x 30 ml), then the organic solutions combined, dried (Na_2SO_4) and evaporated under vacuum to give a brown oil. Chromatography on silica gel (12 g) using a methanol in dichloromethane elution gradient (0-3% methanol) gave an oil, trituration of which with hexane, followed by crystallisation from hexane-ethyl acetate, gave the required mesylate as white crystals (0.19 g, 9%), m. p. 74-76°C. Found: C,55.71; H,6.25; N,11.69. $C_{22}H_{30}N_4O_6S$ requires C,55.21; H,6.32; N,11.71%.

(b) Morpholine (0.19 g, 0.0021 mol) was added to a solution of the above mesylate, namely 5-[5-(2-methanesulphonyloxyethoxymethyl)-2-n-propoxyphenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, (0.20 g, 0.00042 mol) in acetonitrile (25 ml) and the stirred mixture was heated under reflux for 18 hours. The solvent was removed by evaporation under vacuum, the residue dissolved in saturated aqueous sodium carbonate solution and the solution extracted with ethyl acetate (3 x 20 ml). The extracts were combined, dried (Na_2SO_4) and evaporated under vacuum, and the residue was chromatographed on silica gel (4 g) using an elution gradient of methanol in dichloromethane (0-2% methanol). Evaporation under vacuum of the appropriate fractions, followed by crystallisation from hexane, gave the title compound as white crystals (0.098 g, 48%), m.p. 65-66°C. Found: C,64.17; H,7.69; N,14.96. $C_{25}H_{35}N_5O_4$ requires C,63.94; H,7.51; N,14.91%.

EXAMPLE 41

5-(2-Ethoxy-5-methanesulphonamidophenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Methanesulphonyl chloride (0.157 g, 0.00137 mol) was added to a stirred solution of 5-(5-amino-2-ethoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (0.45 g, 0.00137 mol) in dry pyridine (30 ml) at 0°C. The mixture was stirred for 18 hours at room temperature and then evaporated under vacuum. The residue was suspended in saturated aqueous sodium bicarbonate solution (50 ml) and the mixture extracted with dichloromethane (2 x 30 ml). The organic extracts were combined, washed with brine (2 x 30 ml), dried (Na_2SO_4) and evaporated under vacuum. The residue was triturated with ether, chromatographed on silica gel (12 g), eluting with a 98.5:1.5 mixture of dichloromethane and methanol, and the required product crystallised from ethyl acetate-hexane to give the title compound as a white powder (0.32 g, 58%), m.p. 205-206°C. Found: C,53.63; H,5.66; N,17.24. $C_{18}H_{23}N_5O_4S$ requires C, 53.32; H,5.72; N,17.27%.

EXAMPLE 42

5-[2-Ethoxy-5-(3-morpholinopropylsulphonamido)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d] pyrimidin-7-one

The title compound was prepared from 5-(5-amino-2-ethoxyphenyl)1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo

[4,3-d]pyrimidin-7-one and 3-morpholinopropylsulphonyl chloride, following the procedure of Example 41, and was obtained as brown crystals (14%), m.p. 157-159°C. Found: C,55.42; H,6.53; N,16.01. $C_{24}H_{34}N_6O_5S$ requires C,55.58; H,6.61; N,16.21%.

EXAMPLE 43

5-[2-Ethoxy-5-(4-methyl-1-piperazinyl)sulphonamidophenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d] pyrimidin-7-one

The title compound was prepared from 4-methyl-1-piperazinylsulphonyl chloride and 5-(5-amino-2-ethoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimdin-7-one, following the procedure of Example 41, and was obtained as an orange powder (13%), m.p. 152-153°C. Found: C,54.32; H,6.38; N,19.88. $C_{22}H_{31}N_7O_4S$ requires C, 53.97; H,6.38; N,20.03%.

EXAMPLE 44

5-[5-(4-Benzyl-1-piperazinylsulphonamidophenyl)-2-ethoxy]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d] pyrimdin-7-one

4-Benzyl-1-piperazinylsulphonyl chloride (Preparation 19, 0.9 g, 0.0029 mol) was added to a stirred solution of 5-(5-amino-2-ethoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (0.94 g, 0.0029 mol), 4-dimethylaminopyridine (0.050 g, 0.00041 mol) and triethylamine (1.09 g, 0.0108 mol) in dichloromethane (50 ml). The solution was stirred at room temperature for 48 hours and then evaporated under vacuum. The residue was suspended in saturated aqueous sodium bicarbonate solution (50 ml) and the suspension extracted with dichloromethane (3 x 30 ml). The organic extracts were combined, washed succesively with saturated aqueous sodium bicarbonate solution (2 x 20 ml) and brine (3 x 20 ml), dried (Na_2SO_4) and evaporated under vacuum. The residue was chromatographed on silica gel (20 g) using a methanol in dichloromethane elution gradient (0-4% methanol), and the required product crystallised from ethyl acetate-hexane to give the title compound as an off-white powder (0.185 g, 11%). Found: C,58.30; H,6.20; N,16.80. $C_{28}H_{35}N_7O_4S$; $0.5H_20$ requires C,58.52; H,6.31; N,17.06%.

PREPARATION 1

1-Methyl-3-n-propylpyrazole-5-carboxylic acid ethyl ester

A mixture of 3-n-propylpyrazole-5-carboxylic acid ethyl ester (24.1 g, 0.132 mol) (prepared by the method of Chem. Pharm. Bull., 1984, 32, 1568) and dimethyl sulphate (16.8 g, 0.133 mol) were heated to 90°C for 2.5 hours. The mixture was dissolved in dichloromethane and the solution washed with aqueous sodium carbonate solution. The organic phase was separated, dried ($MgSO_4$) and evaporated under vacuum to give a solid. Chromatography on silica gel (300 g), eluting with dichloromethane, gave the product as a colourless oil (20.4 g, 79%). Rf 0.8 (silica, dichloromethane, methanol, acetic acid; 80:20:1).

PREPARATION 2

1-Methyl-3-n-propylpyrazole-5-carboxylic acid

1-Methyl-3-n-propylpyrazole-5-carboxylic acid ethyl ester (20.2 g, 0.10 mol) was suspended in 6N aqueous sodium hydroxide solution (50 ml, 0.30 mol). The mixture was heated to 80°C for 2 hours then diluted with water (50 ml) and acidified with concentrated hydrochloric acid (25 ml). Filtration gave the carboxylic acid as pale brown crystals (12.3 g, 71%), m.p. 150-154°C. Found: C,56.99; H,7.25; N,16.90. $C_8H_{12}N_2O_2$ requires C,57.13; H,7.19; N,16.66%.

PREPARATION 3

1-Methyl-4-nitro-3-n-propylpyrazole-5-carboxylic acid

1-Methyl-3-n-propylpyrazole-5-carboxylic acid (12.1 g, 0.072 mol) was added portionwise to a mixture of oleum (13 ml) and fuming nitric acid (11 ml), keeping the temperature below 60°C. After the addition, the mixture was heated at 60°C overnight and then cooled to room temperature before being poured onto ice; filtration then gave the nitropyrazole as a white solid (11.5 g, 75%), m.p. 124-127°C. Found: C,45.43; N,5.22; N,19.42. $C_8H_{11}N_3O_4$ requires C,

45.57; H,5.20; N,19.71%.

PREPARATION 4

1-Methyl-4-nitro-3-n-propylpyrazole-5-carboxamide

1-Methyl-4-nitro-3-n-propylpyrazole-5-carboxylic acid (11.3 g, 0.053 mol) was added to thionyl chloride (50 ml) and the resulting mixture heated under reflux for 3 hours. The reaction mixture was then cooled and excess thionyl chloride removed by evaporation under vacuum. The oily residue was dissolved in acetone (50 ml) and the solution cautiously added to a mixture of ice (50 g) and concentrated aqueous ammonium hydroxide solution (50 ml). The precipitate was collected by filtration to provide the pyrazolecarboxamide as a pale yellow solid (8.77 g, 78%), m.p. 141-143°C. Found: C,45.22; H,5.71; N,26.12. $C_8H_{12}N_4O_3$ requires C,45.28; H,5.70; N,26.40%.

PREPARATION 5

4-Amino-1-methyl-3-n-propylpyrazole-5-carboxamide

1-Methyl-4-nitro-3-n-propylpyrazole-5-carboxamide (3.45 g, 16.2 mmol) and stannous chloride dihydrate (18.4 g, 81 mmol) were suspende in ethanol and the mixture heated under reflux for 2 hours. The resulting solution was cooled to room temperature, basified to pH 9 by the addition of 2N aqueous sodium hydroxide solution and extracted with dichloromethane (3 x 150 ml). The organic extracts were combined, dried ($MgSO_4$) and evaporated under vacuum. Trituration of the residue with ether gave the aminopyrazole as an off-white solid (2.77 g, 94%), m.p; 98-101°C. Found: C,52.84; H,7.81; N,30.38. $C_8H_{14}N_4O$ requires C,52.73; H,7.74; N,30.75%.

PREPARATION 6

4-(2-Ethoxybenzamido)-1-methyl-3-n-propylpyrazole-5-carboxamide

A solution of 2-ethoxybenzoyl chloride (6.1 g, 33.0 mmol) in dichloromethane (50 ml) was added to a stirred solution of 4-amino-1-methyl-3-n-propylpyrazole-5-carboxamide (3.0 g, 16.4 mmol), 4-dimethylaminopyridine (0.02 g, 0.164 mmol) and triethylamine (3.34 g, 33.0 mmol) in dichloromethane (50 ml) at 0°C. The resulting mixture was allowed to warm to room temperature and stirred for a further 2 hours. The solvent was evaporated under vacuum, the residue dissolved in a 19:1 mixture of dichloromethane and methanol (250 ml), and then the solution washed with 1N hydrochloric acid (100 ml), dried ($MgSO_4$) and evaporated under vacuum. The crude material was chromatographed on silica gel (200 g), eluting with a 97:3 mixture of dichloromethane and methanol, to give a pink solid; crystallisation from ethyl acetate-hexane gave the pyrazole-5-carboxamide as a pale pink solid (2.2 g, 40%), m.p. 153-155°C. Found: C, 61.66; H,6.77; N,16.95. $C_{17}H_{22}N_4O_3$ requires C,61.80; H,6.71; N,16.96%.

PREPARATION 7

5-(2-Ethoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

4-(2-Ethoxybenzamido)-1-methyl-3-n-propylpyrazole-5-carboxamide (223 g, 0.676 mol) was added portionwise to a solution of sodium hydroxide (54 g, 1.35 mol) and 30% hydrogen peroxide solution (224 ml) in water (2000 ml). Ethanol (700 ml) was added and the resulting mixture heated under reflux for 2.5 hours, cooled, then evaporated under vacuum. The resulting solid was treated with 2N hydrochloric acid (380 ml), with external cooling, and the mixture was extracted with dichloromethane (1 x 700 ml, 3 x 200 ml). The combined organic extracts were washed successively with saturated aqueous sodium carbonate solution (3 x 400 ml) and brine (300 ml), then dried (Na_2SO_4) and evaporated under vacuum.

Chromatography of the residue on silica gel (1000 g), using a methanol in dichloromethane elution gradient (0-1% methanol), followed by trituration of the crude product with ether (300 ml), gave the title compound as a colourless solid (152.2 g, 72%), m.p. 143-146°C. Found: C,65.56; H,6.44; N,18.14. $C_{17}H_{20}N_4O_2$ requires C,65.36; H,6.45; N, 17.94%.

PREPARATION 8

5-(5-Bromoacetyl-2-ethoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Aluminium trichloride (12.8 g, 0.096 mol) was added portionwise over 1 hour to a stirred solution of 5-(2-ethoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (10.0 g, 0.032 mol) and bromoacetyl bromide (5.6 ml, 0.064 mol) in dichloromethane (150 ml) at 0°C. After 18 hours at room temperature, the reaction mixture was poured into ice and water (400 g) and the resulting mixture stirred vigorously. The organic phase was separated and the aqueous phase further extracted with dichloromethane (2 x 100 ml). The organic solutions were combined, dried (Na_2SO_4) and evaporated under vacuum to give an off-white solid, trituration of which from ether gave the title compound as a white solid (10.87 g, 78%), m.p. 159-160°C. Found: C,52.54; H,4.88; N,12.78. $C_{19}H_{21}BrN_4O_3$ requires C,52.67; H,4,88; N,12.93%.

PREPARATION 9

1-Methyl-4-(2-n-propoxybenzamido)-3-n-propylpyrazole-5-carboxamide

This amide was prepared from 2-n-propoxybenzoyl chloride following the procedure described in Preparation 6 and was obtained as a pink solid (63%), m.p. 148-149°C. Found: C,62.97; H,7.00; N,16.29. $C_{18}H_{24}N_4O_3$ requires C, 62.77; H,7.02; N,16.27%.

PREPARATION 10

1-Methyl-5-(2-n-propoxyphenyl)-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

1-Methyl-4-(2-n-propoxybenzamido)-3-n-propylpyrazole-5-carboxamide (0.34 g, 0.99 mmol) was added to a stirred mixture of 30% hydrogen peroxide solution (1.0 ml), potassium carbonate (0.54 g, 3.92 mmol), water (10 ml) and ethanol (5 ml). The mixture was heated under reflux for 38 hours and then evaporated under vacuum. The residue was suspended in water (20 ml), then the suspension acidified with 2N hydrochloric acid and extracted with dichloromethane (3 x 20 ml). The extracts were combined, dried (Na_2SO_4) and evaporated under vacuum. The resulting residue was chromatographed on silica gel (6 g), using a methanol in dichloromethane elution gradient (0-1% methanol), to give an oil, successive trituration of which with ether gave the required product as a white solid (0.19 g, 59%), m.p. 111-114°C. Found: C,66.26; H,6.92; N,17.15. $C_{18}H_{22}N_4O_2$ requires C,66.23; H,6.80; N,17.17%.

PREPARATION 11

5-(5-Bromoacetyl-2-n-propylphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Aluminium trichloride (6.0 g, 0.045 mol) was added portionwise to a stirred solution of 1-methyl-5-(2-n-propoxyphenyl)-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (5.0 g, 0.0153 mol) and 2-bromoacetyl chloride (2.5 ml, 0.0303 mol) in dichloromethane (100 ml) at 0°C. The reaction mixture was allowed to warm to room temperature, stirred for 18 hours, heated under reflux for 3 hours and then added cautiously to ice and water (100 g). The resulting mixture was stirred for 1 hour and extracted with dichloromethane (2 x 50 ml). The combined organic extracts were washed with brine (2 x 50 ml), dried (Na_2SO_4), then evaporated under vacuum to give an off-white solid, which was triturated with ether to give the title compound as a white solid (4.1 g, 60%). A small sample was crystallised from ethyl acetate-hexane to give the pure product, m.p. 136-137°C. Found: C,53.82; H,5.24; N,12.57. $C_{20}H_{23}BrN_4O_3$ requires C,53.70; H,5.18; N,12.52%.

PREPARATION 12

5-Acetyl-2-ethoxybenzoic acid methyl ester

Iodoethane (16.4 g, 0.105 mol) was added to a stirred mixture of 5-acetyl-2-hydroxybenzoic acid methyl ester (10 g, 51.5 mmol) and anhydrous potassium carbonate (14.4 g, 0.104 mol) in 2-butanone (200 ml) and the resulting mixture heated under reflux for 3 days. The solvent was removed by evaporation under vacuum and the residue partitioned between water (100 ml) and ethyl acetate (100 ml). The aqueous phase was removed and extracted with further ethyl acetate (4 x 100 ml). The organic solutions were combined, dried (Na_2SO_4) and evaporated under vacuum. The residue was chromatographed on silica gel (130 g), using a methanol in dichloromethane elution gradient (0-1% methanol), to

give the title compound as colourless crystals (10.15 g, 89%), m.p. 50-55°C. Found: C,64.88; H,6.38. $C_{12}H_{14}O_4$ requires C,64.85; H,6.35%.

PREPARATION 13

5-Acetyl-2-ethoxybenzoic acid

A mixture of 5-acetyl-2-ethoxybenzoic acid methyl ester (9.6 g, 0.043 mol), 5M aqueous sodium hydroxide solution (44 ml, 0.217 mol), water (80 ml) and 1,4-dioxan (80 ml) was stirred at room temperature for 18 hours. The solvent was removed by evaporation under vacuum, the residue dissolved in water (100 ml) and the resulting solution acidified to pH 1 with concentrated hydrochloric acid. The aqueous mixture was extracted with ethyl acetate (4 x 100 ml) and the combined extracts dried (Na_2SO_4) and evaporated under vacuum. The resulting solid was crystallised from ethyl acetate to give the title compound as a colourless solid (5.4 g, 60%), m.p. 122-125°C. Found: C,63.20; H,5.81. $C_{11}H_{12}O_4$ requires C,63.45; H,5.81%.

PREPARATION 14

5-Acetyl-2-ethoxybenzoyl chloride

Oxalyl chloride (3.66 g, 0.029 mol) was added dropwise to a stired solution of 5-acetyl-2-ethoxybenzoic acid (3.0 g, 0.014 mol) in dichloromethane (15 ml) and dimethylformamide (0.1 ml). After 3 hours at room temperature, the solvent was removed by evaporation under vacuum and the residue azeotroped with hexane (3 x 30 ml) to give the title compound, which was used without further purification.

PREPARATION 15

4-(5-Acetyl-2-ethoxybenzamido)-1-methyl-3-n-propylpyrazole-5-carboxamide

The title compound was prepared from 5-acetyl-2-ethoxybenzoyl chloride and 4-amino-1-methyl-3-n-propylpyrazole-5-carboxamide following the procedure of Preparation 6, and was obtained as a white solid (60%), m.p. 225-227°C. Found: C,61.35; H,6.25; N,15.07. $C_{19}H_{24}N_4O_4$ requires C,61.28; H,6.50; N,15.04%.

PREPARATION 16

5-(5-Chloromethyl-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo-[4,3-d]pyrimdin-7-one

1-Methyl-5-(2-n-propoxyphenyl)-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (0.80 g, 0.00246 mol) was added portionwise to stirred concentrated hydrochloric acid (10 ml) at room temperature. Paraformaldehyde (0.20 g, 0.00246 mol) was then added and the resulting solution stirred at 120°C for 22 hours. The reaction mixture was cooled and poured into ice and water (50 g), then the resulting mixture extracted with ethyl acetate (3 x 30 ml). The organic extracts were combined, dried (Na_2SO_4) and evaporated under vacuum to give a white solid. Trituration with ether, followed by crystallisation from ethyl acetate-hexane, gave the title compound as colourless crystals (0.65 g, 70%), m.p. 102-104°C. Found: C,60,91; H,6.14; N,14.94. $C_{19}H_{23}ClN_4O_2$ requires C,60.88; H,6.18; N,14.95%.

PREPARATION 17

5-(2-Ethoxy-5-nitrophenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

Concentrated nitric acid (0.5 ml) was added dropwise to a stirred solution of 5-(2-ethoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (2.0 g, 0.0064 mol) in concentrated sulphuric acid (10 ml) at 0°C, and the resulting orange solution was stirred at room temperature for 18 hours. The reaction solution was then added dropwise to stirred ice and water (200 g) and the solid precipitate collected by filtration. This solid was then dissolved in dichloromethane (50 ml) and the solution washed successively with brine (2 x 30 ml) and water (30 ml), dried (Na_2SO_4) and evaporated under vacuum to give a yellow solid. Crystallisation from acetonitrile gave the title compound as yellow needles (1.40 g, 61%), m.p. 214-216°C. Found: C,57.36; H,5.21; N,19.49. $C_{17}H_{19}N_5O_4$ requires C,57.13; H,5.36; N,19.60%.

PREPARATION 18

5-(5-Amino-2-ethoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one

5-(2-Ethoxy-5-nitrophenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (0.64 g, 0.0018 mol) was dissolved in ethanol (50 ml) and the solution stirred with 5% palladium on charcoal catalyst (0.050 g) under hydrogen at room temperature and 50 p.s.i. pressure for 4 hours. The mixture was filtered to remove the catalyst, the filtrate evaporated under vacuum, and the residue triturated with ether to give the title compound as an off-white solid (0.56 g, 95%), m.p. 147-148°C. Found: C,62.63; H,6.60; N,21.57. $C_{17}H_{21}N_5O_2$ requires C,62.36; H,6.47; N,21.39%.

PREPARATION 19

4-Benzyl-1-piperazinylsulphonyl chloride

A solution of 1-benzylpiperazine (20.0 g, 0.114 mol) in acetronitrile (45 ml) was added to a solution of sulphuryl chloride (28 ml, 0.346 mol) in acetonitrile (50 ml) and the mixture heated under reflux for 17 hours, then cooled. The solvent was removed by evaporation under vacuum, then the residue triturated with ether (20 x 50 ml) to yield the title compound (27.8 g, 89%), which was used without further purification.

Biological activity

The following Table illustrates the in vitro activities for a range of the compounds of the invention.

TABLE

IN VITRO PDE INHIBITORY DATA: SELECTIVITY BETWEEN CALCIUM/CALMODULIN (Ca/CAM)-INDEPENDENT cGMP PDE AND cGMP-INHIBITED cAMP PDE			
EXAMPLE	IC_{50} (nM)		SELECTIVITY RATIO
	cGMP	cAMP	
3	2.2	86,000	39,090
4	1.8	63,000	35,000
11	4.9	57,000	11,632
14	1.0	57,000	57,000
15	3.4	75,000	22,058
16	3.7	53,000	14,324
20	3.7	59,000	15,945
25	3.4	84,000	24,705
29	5.5	84,000	15,272
30	1.4	58,000	41,428
31	3.4	56,000	16,470
32	1.4	38,000	27,142
39	5.3	54,000	10,188

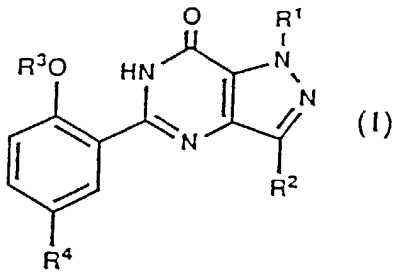
Safety profile

Certain compounds of the invention have been tested at therapeutic doses of up to 1 mg/Kg i.v. and up to 3 mg/Kg p.o. in rats with no signs of adverse acute toxicity being observed. In mice, no deaths occurred after doses of up to 100 mg/Kg i.v.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, PT, SE

1. A compound of formula:



(I)

or a pharmaceutically acceptable salt thereof,
wherein

R^1 is H; C_1-C_3 alkyl optionally substituted with one or more fluoro substituents; or C_3-C_5 cycloalkyl;
R^2 is H, or C_1-C_6 alkyl optionally substituted with one or more fluoro substituents or with C_3-C_6 cycloalkyl;
R^3 is C_1-C_6 alkyl optionally substituted with one or more fluoro substituents or with C_3-C_6 cycloalkyl; C_3-C_5 cycloalkyl; C_3-C_6 alkenyl; or C_3-C_6 alkynyl;
R^4 is C_1-C_4 alkyl optionally substituted with OH, NR^5R^6, CN, $CONR^5R^6$ or CO_2R^7; C_2-C_4 alkenyl optionally substituted with CN, $CONR^5R^6$ or CO_2R^7; C_2-C_4 alkanoyl optionally substituted with NR^5R^6; hydroxy C_2-C_4 alkyl optionally subtituted with NR^5R^6; (C_2-C_3 alkoxy)C_1-C_2 alkyl optionally substituted with OH or NR^5R^6; $CONR^5R^6$; CO_2R^7; halo; NR^5R^6; $NHSO_2NR^5R^6$; $NHSO_2R^8$; or phenyl or heterocyclyl either of which is optionally substituted with methyl;
R^5 and R^6 are each independently H or C_1-C_4 alkyl, or together with the nitrogen atom to which they are attached form a pyrrolidinyl, piperidino, morpholino, 4-(NR^9)-piperazinyl or imidazolyl group wherein said group is optionally substituted with methyl or hydroxy;
R^7 H or C_1-C_4 alkyl;
R^8 is C_1-C_3 alkyl optionally substituted with NR^5R^6;
R^9 H; C_1-C_3 alkyl optionally substituted with phenyl; hydroxy C_2-C_3 alkyl; or C_1-C_4 alkanoyl;

and heterocyclyl means thienyl, pyridyl, pyrazolyl, imidazolyl, triazolyl, oxazolyl, thiazolyl or pyrimidinyl.

2. A compound as claimed in claim 1 wherein R^1 is H, methyl or ethyl; R^2 is C_1-C_3 alkyl; R^3 is C_2-C_3 alkyl; R^4 is C_1-C_2 alkyl optionally substituted with OH, NR^5R^6, $CONR^5R^6$ or CO_2R^7; acetyl optionally substituted with NR^5R^6; hydroxyethyl substituted with NR^5R^6; ethoxymethyl optionally substituted with OH or NR^5R^6; CH=CHCN; $CH=CHCONR^5R^6$; $CH=CHCO_2R^7$; CO_2H; $CONR^5R^6$; Br; NR^5R^6; $NHSO_2NR^5R^6$; $NHSO_2R^8$; or pyridyl or imidazolyl either of which is optionally substituted with methyl; R^5 and R^6 are each independently H, methyl or ethyl, or together with the nitrogen atom to which they are attached form a piperidino, morpholino, 4-(NR^9)-1-piperazinyl or imidazolyl group wherein said group is optionally substituted with methyl or hydroxy; R^7 is H or t-butyl; R^8 is methyl or $CH_2CH_2CH_2NR^5R^6$; and R^9 is H, methyl, benzyl, 2-hydroxyethyl or acetyl.

3. A compound as claimed in claim 2 wherein R^1 is methyl; R^2 is n-propyl; R^3 is ethyl or n-propyl; R^4 is $CH_2NR^5R^6$, $CH_2OCH_2CH_2NR^5R^6$, $CH_2OCH_2CH_3$, $CH_2OCH_2CH_2OH$, $COCH_2NR^5R^6$, $CH(OH)CH_2NR^5R^6$, $CH=CHCON(CH_3)_2$, $CH=CHCO_2R^7$, CO_2H, $CONR^5R^6$, Br, $NHSO_2NR^5R^6$, $NHSO_2CH_2CH_2CH_2NR^5R^6$, 2-pyridyl, 1-imidazolyl or 1-methyl-2-imidazolyl; R^5 and R^6 together with the nitrogen atom to which they are attached form a piperidino, 4-hydroxypiperidino, morpholino, 4-(NR)^9-1-piperazinyl or 2-methyl-1-imidazolyl group; R^7 is H or t-butyl; and R^9 is H, methyl, benzyl, 2-hydroxyethyl or acetyl.

4. A compound as claimed in claim 3 wherein the said compound is selected from:

5-[2-ethoxy-5-(1-methyl-2-imidazolyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-[2-ethoxy-5-(4-methyl-1-piperazinylcarbonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-[5-(4-acetyl-1-piperazinyl)acetyl-2-ethoxyphenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-(2-ethoxy-5-morpholinoacetylphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

and 5-(5-morpholinoacetyl-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one,

and pharmaceutically acceptable salts thereof.

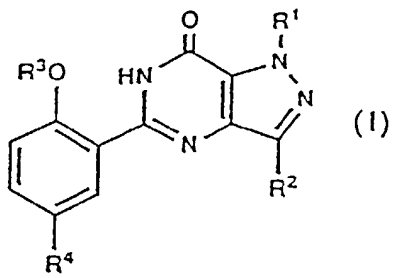
5. A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 4, together with a pharmaceutically acceptable diluent or carrier.

6. A compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, as claimed in any one of claims 1 to 5, for use in medicine.

7. The use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, as claimed in any one of claims 1 to 5, for the manufacture of a medicament for the treatment of stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, stroke, peripheral vascular disease, conditions of reduced blood vessel patency, chronic asthma, bronchitis, allergic asthma, allergic rhinitis, glaucoma or diseases characterised by disorders of gut motility.

Claims for the following Contracting States : ES, GR

1. A process for the preparation of a compound of formula:

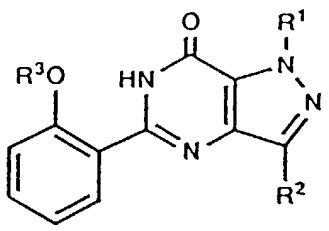


(I)

or a pharmaceutically acceptable salt thereof,
wherein

R^1 is H; C_1-C_3 alkyl optionally substituted with one or more fluoro substituents; or C_3-C_5 cycloalkyl;
R^2 is H, or C_1-C_6 alkyl optionally substituted with one or more fluoro substituents or with C_3-C_6 cycloalkyl;
R^3 is C_1-C_6 alkyl optionally substituted with one or more fluoro substituents or with C_3-C_6 cycloalkyl; C_3-C_5 cycloalkyl; C_3-C_6 alkenyl; or C_3-C_6 alkynyl;
R^4 is C_1-C_4 alkyl optionally substituted with OH, NR^5R^6, CN, $CONR^5R^6$ or CO_2R^7; C_2-C_4 alkenyl optionally substituted with CN, $CONR^5R^6$ or CO_2R^7; C_2-C_4 alkanoyl optionally substituted with NR^5R^6; hydroxy C_2-C_4 alkyl optionally substituted with NR^5R^6; (C_2-C_3 alkoxy)C_1-C_2 alkyl optionally substituted with OH or NR^5R^6; $CONR^5R^6$; CO_2R^7; halo; NR^5R^6; $NHSO_2NR^5R^6$; $NHSO_2R^8$; or phenyl or heterocyclyl either of which is optionally substituted with methyl;
R^5 and R^6 are each independently H or C_1-C_4 alkyl, or together with the nitrogen atom to which they are attached form a pyrrolidinyl, piperidino, morpholino, 4-(NR^9)-piperazinyl or imidazolyl group wherein said group is optionally substituted with methyl or hydroxy;
R^7 is H or C_1-C_4 alkyl;
R^8 is C_1-C_3 alkyl optionally substituted with NR^5R^6;
R^9 is H; C_1-C_3 alkyl optionally substituted with phenyl; hydroxy C_2-C_3 alkyl; or C_1-C_4 alkanoyl;

and heterocyclyl means thienyl, pyridyl, pyrazolyl, imidazolyl, triazolyl, oxazolyl, thiazolyl or pyrimidinyl;
which comprises reacting a compound of formula (II):



(II)

wherein R^1, R^2 and R^3 are as previously defined in this claim, for a compound of formula (I) when R^4 is

(A) C_2-C_4 alkanoyl or hydroxy C_2-C_4 alkyl,
with an acyl halide of formula (C_1-C_3 alkyl)COY wherein Y is halo, in the presence of a Lewis acid, optionally followed by reduction of the resulting ketone to the corresponding alcohol;

(B) C_2-C_4 alkanoyl or hydroxy C_2-C_4 alkyl, each substituted with NR^5R^6 wherein R^5 and R^6 are as previously defined in this claim,
with a haloacyl halide of formula X(C_1-C_3 alkylene)COY wherein X is halo and Y is as previously defined in this claim, in the presence of a Lewis acid, followed by reaction of the resulting haloketone either with an amine of formula R^5R^6NH, optionally followed by reduction of the resulting aminoketone, or with a protected amine of formula R^5NHP, R^6NHP or P'_2NH wherein P and P' are suitable amine protecting groups, optionally followed by reduction of the resulting aminoketone before or after removal of P or P';

(C) C_1-C_4 alkyl optionally substituted with OH,NR^5R^6, $CONR^5R^6$ or CO_2R^7 wherein R^5, R^6 and R^7 are as previously defined in this claim, or bromo,

(i) under chloromethylation conditions, followed by subjection of the resulting chloromethyl intermediate to, respectively,

(a) reduction, or
(b) reaction with an alkali metal hydroxide, or
(c) reaction with an amine of formula R^5R^6NH, or
(d) reaction with an alkali metal cyanide and optionally converting the resulting nitrile to the corresponding amide, acid or ester; or

(ii) under aromatic bromination conditions, followed by subjection of the resulting bromo derivative to, respectively,

(a) lithium-bromine exchange, followed by reaction of the aryllithium derivative with ethylene oxide to give the 2-hydroxyethyl derivative, or
(b) reaction with allyl alcohol, followed by catalytic hydrogenation of the alkene to give the 3-hydroxypropyl derivative, or (c) reaction with 3-buten-1-ol, followed by catalytic hydrogenation of the alkene to give the 4-hydroxybutyl derivative,

and optional conversion of any of the foregoing alcohols to the corresponding alkane, amine or nitrile by activation of their respective hydroxy groups to give the chloride or mesylate followed by reduction, or reaction with an amine of formula R^5R^6NH, or reaction with an alkali metal cyanide, respectively, and further optional conversion of the said nitrile to the corresponding amide or ester;

(D) C_2-C_4 alkenyl 2-substituted with CN, $CONR^5R^6$ or CO_2R^7, or C_2-C_4 alkyl 2-substituted with CN, $CONR^5R^6$, CO_2R^7 or CH_2NH_2, wherein R^5, R^6 and R^7 are as previously defined in this claim,
via the bromo derivative of (C) (ii) above, with the appropriate α, β-unsaturated nitrile, amide or ester respectively, optionally followed by hydrolysis of any resulting ester, reduction of the resulting alkenyl group and, in the case of the nitrile, further or concomitant reduction of the nitrile group to the corresponding primary amine;

(E) C_2-C_4 alkenyl, or C_2-C_4 alkyl, each optionally subsituted with CN, $CONR^5R^6$ or CO_2R^7 wherein R^5, R^6 and

R^7 are as previously defined in this claim,
via the bromo derivative of (C) (ii) above, with a lithium-bromine exchange reagent, followed by subjection of the aryllithium derivative to formylation, and reaction of the resulting aldehyde with the appropriate optionally CN-, $CONR^5R^6$- or CO_2R^7-substituted C_1-C_3 alkyl phosphonium salt or phosphonate, optionally followed by hydrolysis of any resulting ester and reduction of the resulting alkenyl group;

(F) (C_2-C_3 alkoxy)C_1-C_2 alkyl optionally substituted with OH or NR^5R^6 wherein R^5 and R^6 are as previously defined in this claim,

(i) via the chloromethyl derivative of (C) (i) above, with either

(a a C_2- or C_3-alkanol, or
(b) a C_2- or C_3-diol, optionally followed by activation of the hydroxy group to give the mesylate and reaction either with an amine of formula R^5R^6NH, or with a protected amine of formula R^5NHP, R^6NHP or P'_2NH wherein P and P' are as previously defined in this claim; or

(ii) via the bromo derivative of (C) (ii) above, with a lithium-bromine exchange reagent, followed by reaction of the aryllithium derivative with ethylene oxide to give the 2-hydroxyethyl derivative, and activation of the hydroxy group and further reaction as in (i)(a) or (i)(b);

(G) $CONR^5R^6$ or CO_2R^7 wherein R^5, R^6 and R^7 are as previously defined in this claim,
via the bromo derivative of (C) (ii) above, with a lithium-bromine exchange reagent, followed by reaction of the aryllithium derivative with carbon dioxide, and conversion of a suitably activated form of the resulting carboxylic acid to an amide or ester derivative by reaction with an amine of formula R^5R^6NH or alcohol of formula R^7OH respectively ;

(H) NH_2, halo, $NHSO_2NR^5R^6$ or $NHSO_2R^8$ wherein halo is fluoro, chloro, bromo or iodo, and R^5, R^6 and R^8 are as previously defined in this claim,
under aromatic nitration conditions, followed by reduction of the resulting nitro compound to the corresponding primary amine, and subjection of the said amine to, respectively,

(a) a conventional diazotisation-halogenation reaction sequence, or
(b) reaction with either a sulphamoyl halide of formula $R^5R^6NSO_2$halo or a sulphonyl halide of formula R^8SO_2halo, wherein halo is preferably chloro, or reaction with sulphamide when both R^5 and R^6 are H;

(I) phenyl or heterocyclyl, either of which is optionally substituted with methyl,
via the bromo derivative of (C) (ii) above, with either

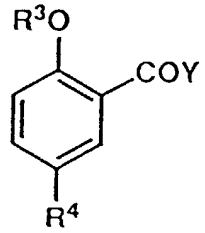
(i) when R^4 is optionally substituted phenyl or C-linked heterocyclyl, the appropriate optionally substituted phenyl or heterocyclyl zincate derivative in the presence of a palladium catalyst, or

(ii) when R^4 is N-linked heterocycle, the appropriate heterocycle in the presence of copper-bronze, iodine and a base;

followed in each case, by optional isolation as, or formation of, a pharmaceutically acceptable salt of the product.

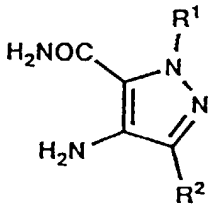
2. A process for the preparation of a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3 and R^4 are as previously defined in claim 1, which comprises reacting a compound of formula (II), wherein R^3 is H and R^1 and R^2 are as previously defined in claim 1, according to any process defined in claim 1 followed by O-alkylation of the phenolic group to introduce R^3 and optional isolation as, or formation of, a pharmaceutically acceptable salt of the product.

3. A process for the preparation of a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3 and R^4 are as previously defined in claim 1, which comprises reacting a compound of formula (X):

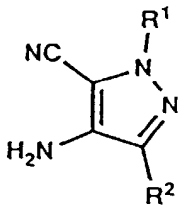


(X)

wherein Y is chloro or bromo, and R^3 and R^4 are as previously defined in claim 1, with an aminopyrazole of either formula (VII) or formula (VIII):



(VII)



(VIII)

wherein R^1 and R^2 are as previously defined in claim 1, followed by cyclisation of the respective resulting amides by treatment with a base, optionally in the presence of hydrogen peroxide, and optional isolation as, or formation of, a pharmaceutically acceptable salt.

4. A process as claimed in claim 1 wherein

in (A), Y is chloro or bromo, the Lewis acid is aluminium chloride or aluminium bromide, and the reducing agent is sodium borohydride;

in (B), X and Y are chloro or bromo, P is benzyl and is removed by catalytic hydrogenation, and P' is t-butoxycarbonyl and is removed using hydrogen chloride;

in (C),

(i) the chloromethylation is carried out using paraformaldehyde and concentrated hydrochloric acid, and

(a) the reduction is effected by palladium-catalysed hydrogenation,
(b) the alkali metal hydroxide is sodium hydroxide or potassium hydroxide,
(c) the reaction with R^5R^6NH is carried out using an excess of said amine,
(d) the alkali metal cyanide is sodium cyanide or potassium cyanide;

(ii) the aromatic bromination is carried out using N-bromosuccinimide, and

(a) the lithium-bromine exchange is effected using n-butyllithium,
(b) the reaction with allyl alcohol is effected under Heck reaction conditions,
(c) the reaction with 3-buten-1-ol is effected under Heck reaction conditions;

in (D), the reaction with the appropriate α,β-unsaturated nitrile, amide or ester respectively, is effected under Heck reaction conditions using tri-o-tolylphosphine, palladium(II) acetate and triethylamine, the optional hydrolysis of the ester is achieved using aqueous sodium hydroxide solution in methanol, the optional reduction of the alkenyl group is effected by palladium-catalysed hydrogenation, and the optional further or concomitant reduction of the nitrile group is carried out using Raney nickel in glacial acetic acid;

in (E), the lithium-bromine exchange is effected using n-butyllithium, the formylation reagent is dimethylformamide, and the alkene reduction is achieved by catalytic hydrogenation;

in (F), the reaction with

(a) a C_2- or C_3-alkanol, is carried out in the presence of one equivalent of sodium metal, or

(b) a C_2- or C_3-diol, is carried out in the presence of one equivalent of sodium metal, the hydroxy group is converted to its mesylate using mesyl chloride in pyridine as solvent, and the reaction with R^5R^6NH is carried out using an excess of said amine; and
(ii) the lithium-bromine exchange is effected using n-butyllithium;

in (G), the lithium-bromine exchange is effected using n-butyllithium, and the carboxylic acid is activated using a carbodiimide in combination with 1-hydroxybenzotriazole;

in (H), the nitration is achieved using concentrated nitric acid in combination with concentrated sulphuric acid, the nitro compound is reduced by catalytic hydrogenation, the reaction with a sulphamoyl chloride or with a sulphonyl chloride is carried out in the presence of excess pyridine or triethylamine optionally in the presence of 4-dimethylaminopyridine, and the reaction with sulphamide is effected at about 100°C;

in (I),

(i) the palladium catalyst is tetrakis(triphenylphosphine)palladium(0), and the optionally substituted phenyl or heterocyclyl zincate derivative is obtained from the corresponding optionally subtituted phenyl or heterocyclyllithium derivative and anhydrous zinc chloride; and

(ii) the heterocyclic is present in excess, and the base is anhydrous potassium carbonate.

5. A process as claimed in claim 2 wherein the O-alkylation is effected using the appropriate alkyl chloride, bromide or sulphonate, in the presence of potassium carbonate.

6. A process as claimed in any one of claims 1 to 5 wherein R^1 is H, methyl or ethyl; R^2 is C_1-C_3 alkyl; R^3 is C_2-C_3 alkyl; R^4 is C_1-C_2 alkyl optionally substituted with OH, NR^5R^6, $CONR^5R^6$ or CO_2R^7; acetyl optionally substituted with NR^5R^6; hydroxyethyl substituted with NR^5R^6; ethoxymethyl optionally substituted with OH or NR^5R^6; CH=CH-CN; $CH=CHCONR^5R^6$; $CH=CHCO_2R^7$; CO_2H; $CONR^5R^6$; Br; NR^5R^6; $NHSO_2NR^5R^6$; $NHSO_2R^8$; or pyridyl or imidazolyl either of which is optionally substituted with methyl; R^5 and R^6 are each independently H, methyl or ethyl, or together with the nitrogen atom to which they are attached form a piperidino, morpholino, 4-(NR^9)-1-piperazinyl or imidazolyl group wherein said group is optionally substituted with methyl or hydroxy; R^7 is H or t-butyl; R^8 is methyl or $CH_2CH_2CH_2NR^5R^6$; and R^9 is H, methyl, benzyl, 2-hydroxyethyl or acetyl.

7. A process as claimed in claim 6 wherein R^1 is methyl; R^2 is n-propyl; R^3 is ethyl or n-propyl; R^4 is $CH_2NR^5R^6$, $CH_2OCH_2CH_2NR^5R^6$, $CH_2OCH_2CH_3$, $CH_2OCH_2CH_2OH$, $COCH_2NR^5R^6$, $CH(OH)CH_2NR^5R^6$, $CH=CHCON(CH_3)_2$, $CH=CHCO_2R^7$, CO_2H, $CONR^5R^6$, Br, $NHSO_2NR^5R^6$, $NHSO_2CH_2CH_2CH_2NR^5R^6$, 2-pyridyl, 1-imidazolyl or 1-methyl-2-imidazolyl; R^5 and R^6 together with the nitrogen atom to which they are attached form a piperidino, 4-hydroxypiperidino, morpholino, 4-(NR^9)-1-piperazinyl or 2-methyl-1-imidazolyl group; R^7 is H or t-butyl; and R^9 is H, methyl, benzyl, 2-hydroxyethyl or acetyl.

8. A process as claimed in claim 7 wherein said compound of formula (I) produced is selected from:

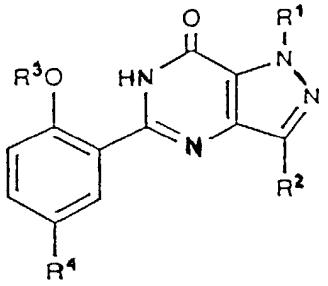
5-[2-ethoxy-5-(1-methyl-2-imidazolyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-[2-ethoxy-5-(4-methyl-1-piperazinylcarbonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-[5-(4-acetyl-1-piperazinyl)acetyl-2-ethoxyphenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-(2-ethoxy-5-morpholinoacetylphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
and 5-(5-morpholinoacetyl-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

and pharmaceutically acceptable salts thereof.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, PT, SE

1. Verbindung der Formel:



(I)

oder ein pharmazeutisch annehmbares Salz hievon, worin R^1 H; C_1-C_3-Alkyl, gegebenenfalls substituiert mit einem oder mehreren Fluor-Substituenten; oder C_3-C_5-Cycloalkyl bedeutet; R^2 H oder C_1-C_6-Alkyl, gegebenenfalls substituiert mit einem oder mehreren Fluor-Substituenten oder mit C_3-C_6-Cycloalkyl, darstellt; R^3 C_1-C_6-Alkyl, gegebenenfalls substituiert mit einem oder mehreren Fluor-Substituenten oder mit C_3-C_6-Cycloalkyl; C_3-C_5-Cycloalkyl; C_3-C_6-Alkenyl oder C_3-C_6-Alkinyl ist; R^4 C_1-C_4-Alkyl, gegebenenfalls substituiert mit OH, NR^5R^6, CN, $CONR^5R^6$ oder CO_2R^7; C_2-C_4-Alkenyl, gegebenenfalls substituiert mit CN, $CONR^5R^6$ oder CO_2R^7; C_2-C_4-Alkanoyl, gegebenenfalls substituiert mit NR^5R^6; Hydroxy-C_2-C_4-alkyl, gegebenenfalls substituiert mit NR^5R^6; (C_2-C_3-Alkoxy)-C_1-C_2-alkyl, gegebenenfalls substituiert mit OH oder NR^5R^6; $CONR^5R^6$; CO_2R^7; Halogen; NR^5R^6; $NHSO_2NR^5R^6$; $NHSO_2R^8$; oder Phenyl oder Heterocyclyl, wobei jedes hievon gegebenenfalls mit Methyl substituiert ist, bedeutet; R^5 und R^6 jeweils unabhängig H oder C_1-C_4-Alkyl darstellen, oder zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine Pyrrolidinyl-, Piperidino-, Morpholino-, 4-(NR^9)-Piperazinyl- oder Imidazolyl-Gruppe bilden, wobei diese Gruppe gegebenenfalls substituiert ist mit Methyl oder Hydroxy; R^7 H oder C_1-C_4-Alkyl bedeutet; R^8 C_1-C_3-Alkyl, gegebenenfalls substituiert mit NR^5R^6, darstellt; R^9 H, C_1-C_3-Alkyl, gegebenenfalls substituiert mit Phenyl; Hydroxy-C_2-C_3-alkyl oder C_1-C_4-Alkanoyl ist; und Heterocyclyl Thienyl, Pyridyl, Pyrazolyl, Imidazolyl, Triazolyl, Oxazolyl, Thiazolyl oder Pyrimidinyl bedeutet.

2. Verbindung nach Anspruch 1, worin R^1 H, Methyl oder Ethyl bedeutet; R^2 C_1-C_3-Alkyl darstellt; R^3 C_2-C_3-Alkyl ist; R^4 C_1-C_2-Alkyl, gegebenenfalls substituiert mit OH, NR^5R^6, $CONR^5R^6$ oder CO_2R^7; Acetyl, gegebenenfalls substituiert mit NR^5R^6; Hydroxyethyl, substituiert mit NR^5R^6; Ethoxymethyl, gegebenenfalls substituiert mit OH oder NR^5R^6; CH=CHCN; $CH=CHCONR^5R^6$; $CH=CHCO_2R^7$; CO_2H; $CONR^5R^6$; Br; NR^5R^6; $NHSO_2NR^5R^6$; $NHSO_2R^8$; oder Pyridyl oder Imidazolyl, wobei jedes hievon gegebenenfalls mit Methyl substituiert ist, bedeutet; R^5 und R^6 jeweils unabhängig H, Methyl oder Ethyl darstellen, oder zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine Piperidino-, Morpholino-, 4-(NR^9)-1-Piperazinyl- oder Imidazolyl-Gruppe bilden, wobei diese Gruppe gegebenenfalls substituiert ist mit Methyl oder Hydroxy; R^7 H oder tert.Butyl bedeutet; R^8 Methyl oder $CH_2CH_2CH_2NR^5R^6$ darstellt; und R^9 H, Methyl, Benzyl, 2-Hydroxyethyl oder Acetyl bedeutet.

3. Verbindung nach Anspruch 2, worin R^1 Methyl bedeutet; R^2 n-Propyl darstellt; R^3 Ethyl oder n-Propyl ist; R^4 $CH_2NR^5R^6$, $CH_2OCH_2CH_2NR^5R^6$, $CH_2OCH_2CH_3$, $CH_2OCH_2CH_2OH$, $COCH_2NR^5R^6$, $CH(OH)CH_2NR^5R^6$, $CH=CHCON(CH_3)_2$, $CH=CHCO_2R^7$, CO_2H, $CONR^5R^6$, Br, $NHSO_2NR^5R^6$, $NHSO_2CH_2CH_2CH_2NR^5R^6$, 2-Pyridyl, 1-Imidazolyl oder 1-Methyl-2-imidazolyl bedeutet; R^5 und R^6 zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine Piperidino-, 4-Hydroxypiperidino-, Morpholino-, 4-(NR^9)-1-Piperazinyl- oder 2-Methyl-1-imidazolyl-Gruppe bilden; R^7 H oder tert.Butyl bedeutet; und R^9 H, Methyl, Benzyl, 2-Hydroxyethyl oder Acetyl darstellt.

4. Verbindung nach Anspruch 3, wobei diese Verbindung ausgewählt ist aus:

5-[2-Ethoxy-5-(1-methyl-2-imidazolyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-on;
5-[2-Ethoxy-5-(4-methyl-1-piperazinylcarbonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-on;
5-[5-(4-Acetyl-1-piperazinyl)-acetyl-2-ethoxyphenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-on;
5-(2-Ethoxy-5-morpholinoacetylphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-on; und
5-(5-Morpholinoacetyl-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-on,
und pharmazeutisch annehmbaren Salzen hievon.

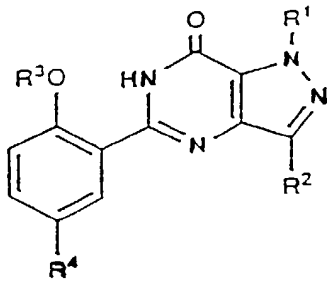
5. Pharmazeutische Zusammensetzung, welche eine Verbindung der Formel (I), oder ein pharmazeutisch annehmbares Salz hievon, nach einem der Ansprüche 1 bis 4 zusammen mit einem pharmazeutisch annehmbaren Verdünnungsmittel oder Träger umfaßt.

6. Verbindung der Formel (I), oder ein pharmazeutisch annehmbares Salz hievon, oder eine pharmazeutische Zusammensetzung, die eine der Einheiten enthält, nach einem der Ansprüche 1 bis 5 zur Verwendung in der Medizin.

7. Verwendung einer Verbindung der Formel (I), oder eines pharmazeutisch annehmbaren Salzes hievon, oder einer pharmazeutischen Zusammensetzung, die eine der Einheiten enthält, nach einem der Ansprüche 1 bis 5 bei der Herstellung eines Medikaments zur Behandlung von stabiler, instabiler und Variant-(Prinzmetal-) Angina, Hypertension, pulmonaler Hypertension, kongestivem Herzversagen, Atherosklerose, Schlaganfall, peripheren Gefäßerkrankungen, Zuständen einer verringerten Durchgängigkeit der Blutgefäße, chromischem Asthma, Bronchitis, allergischem Asthma, allergischer Rhinitis, Glaukom oder durch Störungen der Darmmotilität charakterisierten Erkrankungen.

Patentansprüche für folgende Vertragsstaaten : ES, GR

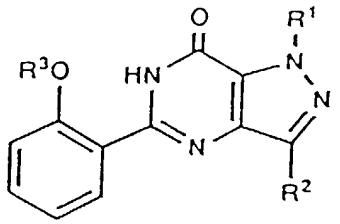
1. Verfahren zur Herstellung einer Verbindung der Formel:



(I)

oder eines pharmazeutisch annehmbaren Salzes hievon, worin R^1 H; C_1-C_3-Alkyl, gegebenenfalls substituiert mit einem oder mehreren Fluor-Substituenten; oder C_3-C_5-Cycloalkyl bedeutet; R^2 H oder C_1-C_6-Alkyl, gegebenenfalls substituiert mit einem oder mehreren Fluor-Substituenten oder mit C_3-C_6-Cycloalkyl, darstellt; R^3 C_1-C_6-Alkyl, gegebenenfalls substituiert mit einem oder mehreren Fluor-Substituenten oder mit C_3-C_6-Cycloalkyl; C_3-C_5-Cycloalkyl, C_3-C_6-Alkenyl oder C_3-C_6-Alkinyl ist; R^4 C_1-C_4-Alkyl, gegebenenfalls substituiert mit OH, NR^5R^6, CN, $CONR^5R^6$ oder CO_2R^7; C_2-C_4-Alkenyl, gegebenenfalls substituiert mit CN, $CONR^5R^6$ oder CO_2R^7; C_2-C_4-Alkanoyl, gegebenenfalls substituiert mit NR^5R^6; Hydroxy-C_2-C_4-alkyl, gegebenenfalls substituiert mit NR^5R^6; (C_2-C_3-Alkoxy)-C_1-C_2-alkyl, gegebenenfalls substituiert mit OH oder NR^5R^6; $CONR^5R^6$; CO_2R^7; Halogen; NR^5R^6; $NHSO_2NR^5R^6$; $NHSO_2R^8$; oder Phenyl oder Heterocyclyl, wobei jedes hievon gegebenenfalls mit Methyl substituiert ist, bedeutet; R^5 und R^6 jeweils unabhängig H oder C_1-C_4-Alkyl darstellen, oder zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine Pyrrolidinyl-, Piperidino-, Morpholino-, 4-(NR^9)-Piperazinyl- oder Imidazolyl-Gruppe bilden, wobei diese Gruppe gegebenenfalls substituiert ist mit Methyl oder Hydroxy; R^7 H oder C_1-C_4-Alkyl bedeutet; R^8 C_1-C_3-Alkyl, gegebenenfalls substituiert mit NR^5R^6, darstellt; R^9 H; C_1-C_3-Alkyl, gegebenenfalls substituiert mit Phenyl; Hydroxy-C_2-C_3-alkyl oder C_1-C_4-Alkanoyl ist; und Heterocyclyl Thienyl, Pyridyl,

Pyrazolyl, Imidazolyl, Triazolyl, Oxazolyl, Thiazolyl oder Pyrimidinyl bedeutet; welches Verfahren umfaßt: Umsetzen einer Verbindung der Formel (II):



(II),

worin R^1, R^2 und R^3 wie vorstehend in diesem Anspruch für eine Verbindung der Formel (I) definiert sind, wenn R^4 bedeutet:

(A) C_2-C_4-Alkanoyl oder Hydroxy-C_2-C_4-alkyl, mit einem Acylhalogenid der Formel (C_1-C_3-Alkyl)COY, wobei Y Halogen darstellt, in Anwesenheit einer Lewis-Säure, gegebenenfalls gefolgt von einer Reduktion des erhaltenen Ketons zum entsprechenden Alkohol;

(B) C_2-C_4-Alkanoyl oder Hydroxy-C_2-C_4-alkyl, jeweils substituiert mit NR^5R^6, wobei R^5 und R^6 wie vorstehend in diesem Anspruch definiert sind, mit einem Halogenacylhalogenid der Formel X(C_1-C_3-Alkylen)COY, wobei X Halogen darstellt, und Y wie vorstehend in diesem Anspruch definiert ist, in Anwesenheit einer Lewis-Säure, gefolgt vom Umsetzen des erhaltenen Halogenketons entweder mit einem Amin der Formel R^5R^6NH, gegebenenfalls gefolgt von der Reduktion des erhaltenen Aminoketons, oder mit einem geschützten Amin der Formel R^5NHP, R^6NHP oder P'_2NH, wobei P und P' geeignete Amin-Schutzgruppen sind, gegebenenfalls gefolgt von der Reduktion des erhaltenen Aminoketons vor oder nach der Entfernung von P oder P';

(C) C_1-C_4-Alkyl, gegebenenfalls substituiert mit OH, NR^5R^6, $CONR^5R^6$ oder CO_2R^7, wobei R^5, R^6 und R^7 wie vorstehend in diesem Anspruch definiert sind, oder Brom,

(i) unter Chlormethylierungsbedingungen, gefolgt vom Unterwerfen der erhaltenen Chlormethyl-Zwischenverbindung jeweils

(a) einer Reduktion, oder
(b) einem Umsetzen mit einem Alkalimetallhydroxid, oder
(c) einem Umsetzen mit einem Amin der Formel R^5R^6NH, oder
(d) einem Umsetzen mit einem Alkalimetallcyanid, und gegebenenfalls einem Überführen des erhaltenen Nitrils in das entsprechende Amid, die Säure oder den Ester; oder

(ii) unter aromatischen Bromierungsbedingungen, gefolgt vom Unterwerfen des erhaltenen Brom-Derivats jeweils

(a) einem Lithium-Brom-Austausch, gefolgt vom Umsetzen des Aryllithium-Derivats mit Ethylenoxid, wobei das 2-Hydroxyethyl-Derivat erhalten wird, oder
(b) einem Umsetzen mit Allylalkohol, gefolgt von katalytischer Hydrierung des Alkens, wobei das 3-Hydroxypropyl-Derivat erhalten wird, oder
(c) einem Umsetzen mit 3-Buten-1-ol, gefolgt von katalytischer Hydrierung des Alkens, wobei das 4-Hydroxybutyl-Derivat erhalten wird, und gegebenenfalls Überführen irgendeines der vorstehenden Alkohole in das entsprechende Alkan, Amin oder Nitril durch die Aktivierung ihrer entsprechenden Hydroxy-Gruppen, wobei das Chlorid oder Mesylat erhalten wird, gefolgt von einer Reduktion, oder einem Umsetzen mit einem Amin der Formel R^5R^6NH, bzw. einem Umsetzen mit einem Alkalimetallcyanid und einer weiteren gegebenenfalls durchgeführten Überführung des Nitrils in das entsprechende Amid oder den Ester;

(D) C_2-C_4-Alkenyl, 2-substituiert mit CN, $CONR^5R^6$ oder CO_2R^7, oder C_2-C_4-Alkyl, 2-substituiert mit CN, $CONR^5R^6$, CO_2R^7 oder CH_2NH_2, wobei R^5, R^6 und R^7 wie vorstehend in diesem Anspruch definiert sind, über das Brom-Derivat von (C)(ii) oben, mit dem geeigneten α,β-ungesättigten Nitril, Amid bzw. Ester, gegebenenfalls gefolgt von einer Hydrolyse irgendeines erhaltenen Esters, Reduktion der erhaltenen Alkenyl-Gruppe und, im Fall des Nitrils, weiterer oder gleichzeitiger Reduktion der Nitril-Gruppe zum entsprechenden primären

Amin;
(E) C_2-C_4-Alkenyl oder C_2-C_4-Alkyl, jeweils gegebenenfalls substituiert mit CN, $CONR^5R^6$ oder CO_2R^7, wobei R^5, R^6 und R^7 wie vorstehend in diesem Anspruch definiert sind, über das Brom-Derivat von (C)(ii) oben, mit einem Lithium-Brom-Austauschreagens, gefolgt vom Unterwerfen des Aryllithium-Derivats einer Formylierung, und Umsetzen des erhaltenen Aldehyds mit dem geeigneten, gegebenenfalls CN-, $CONR^5R^6$- oder CO_2R^7-substituierten, C_1-C_3-Alkylphosphoniumsalz oder Phosponat, gegebenenfalls gefolgt von einer Hydrolyse irgendeines erhaltenen Esters und Reduktion der erhaltenen Alkenyl-Gruppe;
(F) (C_2-C_3-Alkoxy)-C_1-C_2-alkyl, gegebenenfalls substituiert mit OH oder NR^5R^6, wobei R^5 und R^6 wie vorstehend in diesem Anspruch definiert sind,

(i) über das Chlormethyl-Derivat von (C)(i) oben, entweder mit

(a) einem C_2- oder C_3-Alkanol oder
(b) einem C_2- oder C_3-Diol, gegebenenfalls gefolgt von einer Aktivierung der Hydroxy-Gruppe, wobei das Mesylat erhalten wird, und einem Umsetzen entweder mit einem Amin der Formel R^5R^6NH oder mit einem geschützten Amin der Formel R^5NHP, R^6NHP oder P'_2NH, wobei P und P' wie vorstehend in diesem Anspruch definiert sind; oder

(ii) über das Brom-Derivat von (C)(ii) oben, mit einem Lithium-Brom-Austauschreagens, gefolgt von einem Umsetzen des Aryllithium-Derivats mit Ethylenoxid, wobei das 2-Hydroxyethyl-Derivat erhalten wird, und einer Aktivierung der Hydroxy-Gruppe und einem weiteren Umsetzen wie in (i)(a) oder (i)(b);

(G) $CONR^5R^6$ oder CO_2R^7, wobei R^5, R^6 und R^7 wie vorstehend in diesem Anspruch definiert sind, über das Brom-Derivat von (C)(ii) oben, mit einem Lithium-Brom-Austauschreagens, gefolgt von einem Umsetzen des Aryllithium-Derivats mit Kohlendioxid, und Überführen einer geeignet aktivierten Form der erhaltenen Carbonsäure in ein Amid- oder Ester-Derivat durch das Umsetzen mit einem Amin der Formel R^5R^6NH bzw. Alkohol der Formel R^7OH;
(H) NH_2, Halogen, $NHSO_2NR^5R^6$ oder $NHSO_2R^8$, wobei Halogen Fluor, Chlor, Brom oder Iod bedeutet, und R^5, R^6 und R^8 wie vorstehend in diesem Anspruch definiert sind, unter aromatischen Nitrierungsbedingungen, gefolgt von einer Reduktion der erhaltenen Nitro-Verbindung zum entsprechenden primären Amin, und Unterwerfen des Amins jeweils

(a) einer herkömmlichen Diazotierungs-Halogenierungs-Sequenz, oder
(b) einem Umsetzen entweder mit einem Sulfamoylhalogenid der Formel $R^5R^6NSO_2$Halogen oder einem Sulfonylhalogenid der Formel R^8SO_2Halogen, wobei Halogen vorzugsweise Chlor bedeutet, oder einem Umsetzen mit Sulfamid, wenn sowohl R^5 als auch R^6 H darstellen;

(I) Phenyl oder Heterocyclyl, wobei jedes hievon gegebenenfalls mit Methyl substituiert ist, über das Brom-Derivat von (C)(ii) oben, entweder mit

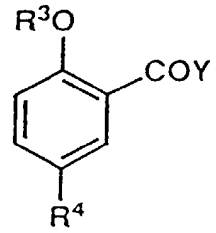
(i) wenn R^4 gegebenenfalls substituiertes Phenyl oder C-gebundenes Heterocyclyl ist, dem geeigneten, gegebenenfalls substituierten, Phenyl- oder Heterocyclylzinkat-Derivat in Anwesenheit eines Palladium-Katalysators, oder
(ii) wenn R^4 ein N-gebundener Heterocyclus ist, dem geeigneten Heterocyclus in Anwesenheit von Kupfer-Bronze, Iod und einer Base;

gefolgt in jedem Fall von der gegebenenfalls durchgeführten Isolierung als pharmazeutisch annehmbares Salz des Produkts oder Bildung desselben.

2. Verfahren zur Herstellung einer Verbindung der Formel (I), oder eines pharmazeutisch annehmbaren Salzes hievon, worin R^1, R^2, R^3 und R^4 wie vorstehend in Anspruch 1 definiert sind, welches umfaßt: Umsetzen einer Verbindung der Formel (II), worin R^3 die Bedeutung H hat, und R^1 und R^2 wie vorstehend in Anspruch 1 definiert sind, gemäß einem beliebigen in Anspruch 1 definierten Verfahren, gefolgt von einer O-Alkylierung der Phenol-Gruppe zur Einführung von R^3 und der gegebenenfalls durchgeführten Isolierung eines pharmazeutisch annehmbaren Salzes des Produkts oder Bildung desselben.

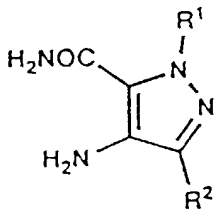
3. Verfahren zur Herstellung einer Verbindung der Formel (I), oder eines pharmazeutisch annehmbaren Salzes hievon, worin R^1, R^2, R^3 und R^4 wie vorstehend in Anspruch 1 definiert sind, welches umfaßt: Umsetzen einer Ver-

bindung der Formel (X):

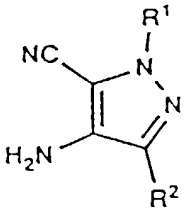


(X),

worin Y Chlor oder Brom bedeutet, und R^3 und R^4 wie vorstehend in Anspruch 1 definiert sind, mit einem Aminopyrazol entweder der Formel (VII) oder der Formel (VIII):



(VII)



(VIII),

worin R^1 und R^2 wie vorstehend in Anspruch 1 definiert sind, gefolgt von der Cyclisierung der entsprechenden erhaltenen Amide durch die Behandlung mit einer Base, gegebenenfalls in Anwesenheit von Wasserstoffperoxid, und der gegebenenfalls durchgeführten Isolierung als pharmazeutisch annehmbares Salz oder Bildung desselben.

4. Verfahren nach Anspruch 1, wobei

in (A) Y Chlor oder Brom bedeutet, die Lewis-Säure Aluminiumchlorid oder Aluminiumbromid ist, und das Reduktionsmittel Natriumborhydrid ist;
in (B) X und Y Chlor oder Brom bedeuten, P Benzyl darstellt und durch katalytische Hydrierung entfernt wird, und P' tert.Butoxycarbonyl ist und unter Verwendung von Chlorwasserstoff entfernt wird;
in (C)

(i) die Chlormethylierung unter Verwendung von Paraformaldehyd und konzentrierter Salzsäure durchgeführt wird, und

(a) die Reduktion durch Palladium-katalysierte Hydrierung bewirkt wird,
(b) das Alkalimetallhydroxid Natriumhydroxid oder Kaliumhydroxid ist,
(c) das Umsetzen mit R^5R^6NH unter Verwendung eines Überschusses des Amins durchgeführt wird,
(d) das Alkalimetallcyanid Natriumcyanid oder Kaliumcyanid ist;

(ii) die aromatische Bromierung unter Verwendung von N-Bromsuccinimid durchgeführt wird, und

(a) der Lithium-Brom-Austausch unter Verwendung von n-Butyllithium bewirkt wird,
(b) das Umsetzen mit Allylalkohol unter Heck-Reaktionsbedingungen durchgeführt wird,
(c) das Umsetzen mit 3-Buten-1-ol unter Heck-Reaktionsbedingungen bewirkt wird;

in (D) das Umsetzen mit dem geeigneten α,β-ungesättigten Nitril, Amid bzw. Ester unter Heck-Reaktionsbedingungen unter Verwendung von Tri-o-tolylphosphin, Palladium(II)-acetat und Triethylamin durchgeführt wird, die gegebenenfalls vorgenommene Hydrolyse des Esters unter Verwendung wässeriger Natriumhydroxid-Lösung in Methanol erzielt wird, die gegebenenfalls durchgeführte Reduktion der Alkenyl-Gruppe durch Palladium-katalysierte Hydrierung bewirkt wird, und die gegebenenfalls vorgenommene weitere oder gleichzeitige

Reduktion der Nitril-Gruppe unter Verwendung von Raney-Nickel in Eisessig durchgeführt wird;
in (E) der Lithium-Brom-Austausch unter Verwendung von n-Butyllithium durchgeführt wird, das Formylierungsreagens Dimethylformamid ist, und die Alken-Reduktion durch katalytische Hydrierung erzielt wird;
in (F) das Umsetzen mit

(a) einem C_2- oder C_3-Alkanol in Anwesenheit von einem Äquivalent Natriummetall durchgeführt wird, oder
(b) einem C_2- oder C_3-Diol in Anwesenheit von einem Äquivalent Natriummetall durchgeführt wird, die Hydroxy-Gruppe unter Verwendung von Mesylchlorid in Pyridin als Lösungsmittel in ihr Mesylat übergeführt wird, und das Umsetzen mit R^5R^6NH unter Verwendung eines Überschusses des Amins durchgeführt wird; und
(ii) der Lithium-Brom-Austausch unter Verwendung von n-Butyllithium durchgeführt wird;

in (G) der Lithium-Brom-Austausch unter Verwendung von n-Butyllithium durchgeführt wird, und die Carbonsäure unter Verwendung eines Carbodiimids in Kombination mit 1-Hydroxybenzotriazol aktiviert wird;
in (H) die Nitrierung unter Verwendung konzentrierter Salpetersäure in Kombination mit konzentrierter Schwefelsäure erzielt wird, die Nitro-Verbindung durch katalytische Hydrierung reduziert wird, das Umsetzen mit einem Sulfamoylchlorid oder mit einem Sulfonylchlorid in Anwesenheit eines Pyridin- oder Triethylamin-Überschusses, gegebenenfalls in Anwesenheit von 4-Dimethylaminopyridin, durchgeführt wird, und das Umsetzen mit Sulfamid bei etwa 100°C bewirkt wird;
in (I) der Palladium-Katalysator Tetrakis-(triphenylphosphin)-palladium(0) ist, und das gegebenenfalls substituierte Phenyl- oder Heterocyclylzinkat-Derivat aus dem entsprechenden gegebenenfalls substituierten Phenyl- oder Heterocyclyllithium-Derivat und wasserfreiem Zinkchlorid erhalten wird; und
(ii) der Heterocyclus im Überschuß vorhanden ist, und die Base wasserfreies Kaliumcarbonat ist.

5. Verfahren nach Anspruch 2, bei welchem die O-Alkylierung unter Verwendung des geeigneten Alkylchlorids, Bromids oder Sulfonats in Anwesenheit von Kaliumcarbonat durchgeführt wird.

6. Verfahren nach einem der Ansprüche 1 bis 5, wobei R^1 H, Methyl oder Ethyl bedeutet; R^2 C_1-C_3-Alkyl darstellt; R^3 C_2-C_3-Alkyl ist; R^4 C_1-C_2-Alkyl, gegebenenfalls substituiert mit OH, NR^5R^6, $CONR^5R^6$ oder CO_2R^7; Acetyl, gegebenenfalls substituiert mit NR^5R^6; Hydroxyethyl, substituiert mit NR^5R^6; Ethoxymethyl, gegebenenfalls substituiert mit OH oder NR^5R^6; CH=CHCN; CH=CHCONR^{5}R^6; CH=CHCO$_2$R^7; CO_2H; $CONR^5R^6$; Br; NR^5R^6; $NHSO_2NR^5R^6$; $NHSO_2R^8$; oder Pyridyl oder Imidazolyl, wobei jedes hievon gegebenenfalls mit Methyl substituiert ist; bedeutet; R^5 und R^6 jeweils unabhängig H, Methyl oder Ethyl darstellen, oder zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine Piperidino-, Morpholino-, 4-(NR^9)-1-Piperazinyl- oder Imidazolyl-Gruppe bilden, wobei diese Gruppe gegebenenfalls substituiert ist mit Methyl oder Hydroxy; R^7 H oder tert.Butyl bedeutet; R^8 Methyl oder $CH_2CH_2CH_2NR^5R^6$ darstellt; und R^9 H, Methyl, Benzyl, 2-Hydroxyethyl oder Acetyl bedeutet.

7. Verfahren nach Anspruch 6, wobei R^1 Methyl bedeutet; R^2 n-Propyl darstellt; R^3 Ethyl oder n-Propyl ist; R^4 $CH_2NR^5R^6$, $CH_2OCH_2CH_2NR^5R^6$, $CH_2OCH_2CH_3$, $CH_2OCH_2CH_2OH$, $COCH_2NR^5R^6$, $CH(OH)CH_2NR^5R^6$, $CH{=}CHCON(CH_3)_2$, CH=CHCO$_2$R^7, CO_2H, $CONR^5R^6$, Br, $NHSO_2NR^5R^6$, $NHSO_2CH_2CH_2CH_2NR^5R^6$, 2-Pyridyl, 1-Imidazolyl oder 1-Methyl-2-imidazolyl bedeutet; R^5 und R^6 zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine Piperidino-, 4-Hydroxypiperidino-, Morpholino-, 4-(NR^9)-1-Piperazinyl- oder 2-Methyl-1-imidazolyl-Gruppe bilden; R^7 H oder tert.Butyl bedeutet; und R^9 H, Methyl, Benzyl, 2-Hydroxyethyl oder Acetyl darstellt.

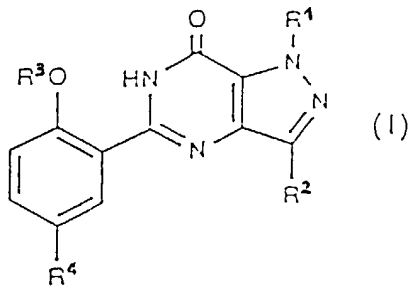
8. Verfahren nach Anspruch 7, wobei die hergestellte Verbindung der Formel (I) ausgewählt wird aus:

5-[2-Ethoxy-5-(1-methyl-2-imidazolyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-on;
5-[2-Ethoxy-5-(4-methyl-1-piperazinylcarbonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-on;
5-[5 -(4-Acetyl-1-piperazinyl)-acetyl-2-ethoxyphenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-on;
5-(2-Ethoxy-5-morpholinoacetylphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-on; und
5-(5-Morpholinoacetyl-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-on,
und pharmazeutisch annehmbaren Salzen hievon.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, PT, SE

1. Composé de formule :



(I)

ou sel pharmaceutiquement acceptable d'un tel composé, dans lequel :

R^1 représente H ; alkyle en C_1-C_3 facultativement substitué par un ou plusieurs substituants fluoro ; ou cycloalkyle en C_3-C_5 ;
R^2 représente H, ou alkyle en C_1-C_6 facultativement substitué par un ou plusieurs substituants fluoro ou par cycloalkyle en C_3-C_6 ;
R^3 représente alkyle en C_1-C_6 facultativement substitué par un ou plusieurs substituants fluoro ou par cycloalkyle en C_3-C_6 ; cycloalkyle en C_3-C_5 ; alkényle en C_3-C_6 ; ou alkynyle en C_3-C_6 ;
R^4 représente alkyle en C_1-C_4 facultativement substitué par OH, NR^5R^6, CN, $CONR^5R^6$ ou CO_2R^7 ; alkényle en C_2-C_4 facultativement substitué par CN, $CONR^5R^6$ ou CO^2R^7 ; alcanoyle en C_2-C_4 facultativement substitué par NR^5R^6 ; hydroxy(alkyle en C_2-C_4) facultativement substitué par NR^5R^6 ; (alcoxy en C_2-C_3)alkyle en C_1-C_2 facultativement substitué par OH ou NR^5R^6 ; $CONR^5R^6$; CO_2R^7 ; halogéno ; NR^5R^6 ; $NHSO_2NR^5R^6$; $NHSO_2R^8$; phényle ou hétérocyclyle dont l'un ou l'autre est facultativement substitué par méthyle ;
R^5 et R^6 représentent chacun indépendamment H ou alkyle en C_1-C_4 ou, pris ensemble avec l'atome d'azote auquel ils sont liés, forment un groupe pyrrolidinyle, pipéridino, morpholino, 4-(NR^9)-pipérazinyle ou imidazolyle, ledit groupe étant facultativement substitué par méthyle ou hydroxy ;
R^7 représente H ou alkyle en C_1-C_4 ;
R^8 représente alkyle en C_1-C_3 facultativement substitué par NR^5R^6 ;
R^9 représente H ; alkyle en C_1-C_3 facultativement substitué par phényle ; hydroxyalkyle en C_2-C_3 ; ou alcanoyle en C_1-C_4 ; et

hérétocyclyle signifie thiényle, pyridyle, pyrazolyle, imidazolyle, triazolyle, oxazolyle, thiazolyle ou pyrimidinyle.

2. Composé selon la revendication 1 dans lequel R^1 représente H, méthyle ou éthyle R^2 représente alkyle en C_1-C_3 ; R^3 représente alkyle en C_2-C_3 ; R^4 représente alkyle en C_1-C_2 facultativement substitué par OH, NR^5R^6, $CONR^5R^6$ ou CO_2R^7 ; acétyle facultativement substitué par NR^5R^6 ; hydroxyéthyle substitué par NR^5R^6 ; éthoxyméthyle facultativement substitué par OH ou NR^5R^6 ; CH=CHCN ; $CH=CHCONR^5R^6$; $CH=CHCO_2R^7$; CO_2H ; $CONR^5R^6$; Br ; NR^5R^6 ; $NHSO_2NR^5R^6$; $NHSO_2R^8$; ou pyridyle ou imidazolyle dont l'un ou l'autre est facultativement substitué par méthyle ; R^5 et R^6 sont chacun indépendamment choisis entre H, méthyle ou éthyle, ou pris ensemble avec l'atome d'azote auquel ils sont liés forment un groupe pipéridino, morpholino, 4-(NR^9)-1-pipérazinyle ou imidazolyle, ledit groupe étant facultativement substitué par méthyle ou hydroxy ; R^7 représente H ou t-butyle ; R^8 représente méthyle ou $CH_2CH_2CH_2NR^5R^6$; et R^9 représente H, méthyle, benzyle, 2-hydroxyéthyle ou acétyle.

3. Composé selon la revendication 2 dans lequel R^1 représente méthyle ; R^2 représente n-propyle ; R^3 représente éthyle ou n-propyle ; R^4 représente $CH_2NR^5R^6$, $CH_2OCH_2CH_2NR^5R^6$, $CH_2OCH_2CH_3$, $CH_2OCH_2CH_2OH$, $COCH_2NR^5R^6$, $CH(OH)CH_2NR^5R^6$, $CH=CHCON(CH_3)_2$, $CH=CHCO_2R^7$, CO_2H, $CONR^5R^6$, Br, $NHSO_2NR^5R^6$, $NHSO_2CH_2CH_2CH_2NR^5R^6$, 2-pyridyle, 1-imidazolyle ou 1-méthyl-2-imidazolyle ; R^5 et R^6 pris ensemble avec l'ato-

me d'azote auquel ils sont liés forment un groupe pipéridino, 4-hydroxypipéridino, morpholino, 4- (NR^9) -1-pipérazinyle ou 2-méthyl-1-imidazolyle ; R^7 représente H ou t-butyle ; et R^9 représente H, méthyle, benzyle, 2-hydroxyéthyle ou acétyle.

4. Composé selon la revendication 3, qui est choisi parmi :

la 5-[2-éthoxy-5-(1-méthyl-2-imidazolyl)phényl]-1-méthyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one ;
la 5-[2-éthoxy-5-(4-méthyl-1-pipérazinylcarbonyl)-phényl]-1-méthyl-3-n-propyl-1,6-dihydro-7H-pyrazolo [4,3-d]pyrimidin-7-one ;
la 5-[5-(4-acétyl-1-pipérazinyl)acétyl-2-éthoxyphényl]-1-méthyl-3-n-propyl-1,6-dihydro-7H-pyrazolo-[4,3-d] pyrimidin-7-one ;
la 5-(2-éthoxy-5-morpholinoacétylphényl)-1-méthyl-3-n-propyl-1,6-dihydro-7H-pyrazolo-[4,3-d]pyrimidin-7-one ; et
la 5-(5-morpholinoacétyl-2-n-propoxyphényl)-1-méthyl-3-n-propyl-1,6-dihydro-7H-pyrazolo-[4,3-d]pyrimidin-7-one, et leurs sels pharmaceutiquement acceptables.

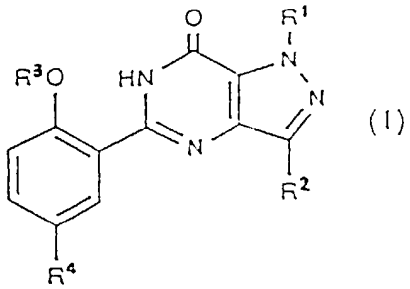
5. Composition pharmaceutique comprenant un composé de formule (I), ou un sel pharmaceutiquement acceptable d'un tel composé, selon l'une quelconque des revendications 1 à 4, avec un diluant ou un véhicule pharmaceutiquement acceptable.

6. Composé de formule (I), ou sel pharmaceutiquement acceptable d'un tel composé, ou composition pharmaceutique contenant ledit composé ou ledit sel, selon l'une quelconque des revendications 1 à 5, pour une utilisation en médecine.

7. Utilisation d'un composé de formule (I), ou d'un sel pharmaceutiquement acceptable d'un tel composé, ou composition pharmaceutique contenant ledit composé ou ledit sel, selon l'une quelconque des revendications 1 à 5, pour la fabrication d'un médicament en vue du traitement de l'angor stable, instable ou variant (Prinzmetal), de l'hypertension, de l'hypertension pulmonaire, de la défaillance cardiaque congestive, de l'athérosclérose, des attaques, de la maladie vasculaire périphérique, des états de libre passage entravé des vaisseaux sanguins, d'asthme chronique, de bronchite, d'asthme allergique, de rhinite allergique, de glaucome ou de maladies caractérisées par des désordres de la motilité intestinale.

Revendications pour les Etats contractants suivants : ES, GR

1. Procédé de préparation d'un composé de formule :



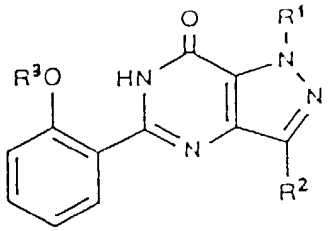
(I)

ou d'un sel pharmaceutiquement acceptable d'un tel composé, dans lequel:

R^1 représente H ; alkyle en C_1-C_3 facultativement substitué par un ou plusieurs substituants fluoro ; ou cycloalkyle en C_3-C_5 ;
R^2 représente H, ou alkyle en C_1-C_6 facultativement substitué par un ou plusieurs substituants fluoro ou par cycloalkyle en C_3-C_6 ;
R^3 représente alkyle en C_1-C_6 facultativement substitué par un ou plusieurs substituants fluoro ou par cycloalkyle en C_3-C_6 ; cycloalkyle en C_3-C_5 ; alkényle en C_3-C_6 ; ou alkynyle en C_3-C_6 ;

R^4 représente alkyle en C_1-C_4 facultativement substitué par OH, NR^5R^6, CN, $CONR^5R^6$ ou CO_2R^7 ; alkényle en C_2-C_4 facultativement substitué par CN, $CONR^5R^6$ ou CO_2R^7 ; alcanoyle en C_2-C_4 facultativement substitué par NR^5R^6 ; hydroxy(alkyle en C_2-C_4) facultativement substitué par NR^5R^6 ; (alcoxy en C_2-C_3)alkyle en C_1-C_2 facultativement substitué par OH ou NR^5R^6 ; $CONR^5R^6$; CO_2R^7 ; halogéno ; NR^5R^6 ; $NHSO_2NR^5R^6$; $NHSO_2R^8$; phényle ou hétérocyclyle dont l'un ou l'autre est facultativement substitué par méthyle ;
R^5 et R^6 représentent chacun indépendamment H ou alkyle en C_1-C_4 ou, pris ensemble avec l'atome d'azote auquel ils sont liés, forment un groupe pyrrolidinyle, pipéridino, morpholino, 4-(NR^9)-pipérazinyle ou imidazolyle, ledit groupe étant facultativement substitué par méthyle ou hydroxy ;
R^7 représente H ou alkyle en C_1-C_4 ;
R^8 représente alkyle en C_1-C_3 facultativement substitué par NR^5R^6 ;
R^9 représente H ; alkyle en C_1-C_3 facultativement substitué par phényle ; hydroxyalkyle en C_2-C_3 ; ou alcanoyle en C_1-C_4 ; et
hérétocyclyle signifie thiényle, pyridyle, pyrazolyle, imidazolyle, triazolyle, oxazolyle, thiazolyle ou pyrimidinyle ;

qui consiste à faire réagir un composé de formule (II)



(II)

dans laquelle R^1, R^2 et R^3 sont tels que précédemment définis dans cette revendication, pour un composé de formule (I),
lorsque R^4 représente :

(A) alcanoyle en C_2-C_4 ou hydroxyalkyle en C_2-C_4, avec un halogénure d'acyle de formule (alkyle en C_1-C_3) COY dans laquelle Y représente halogéno, en présence d'un acide de Lewis, facultativement suivie par la réduction de la cétone résultante en alcool correspondant.
(B) alcanoyle en C_2-C_4 ou hydroxyalkyle en C_2-C_4, dont chacun est substitué par NR^5R^6 où R^5 et R^6 sont tels que précédemment définis dans cette revendication, avec un halogénure d'halogénoacyle de formule X(alkylène en C_1-C_3)COY dans laquelle X représente halogéno et Y est tel que précédemment défini dans cette revendication, en présence d'un acide de Lewis, suivie par la réaction de l'halogénocétone résultante, soit avec une amine de formule R^5R^6NH, facultativement suivie par la réduction de l'aminocétone résultante, soit avec une amine protégée de formule R^5NHP, R^6NHP ou P'_2NH où P et P' sont des groupes amino-protecteurs convenables, facultativement suivie par la réduction de l'aminocétone résultante avant ou après l'élimination de P ou de P' ;
(C) alkyle en C_1-C_4 facultativement substitué par OH, NR^5R^6, $CONR^5R^6$ ou CO_2R^7 où R^5, R^6 et R^7 sont tels que précédemment définis dans cette revendication, ou bromo,

(i) dans des conditions de chlorométhylation, suivie de la soumission de l'intermédiaire chlorométhyle résultant à, respectivement,

(a) une réduction, ou
(b) une réaction avec un hydroxyde de métal alcalin, ou
(c) une réaction avec une amine de formule R^5R^6NH, ou
(d) une réaction avec un cyanure de métal alcalin et facultativement la transformation du nitrile résultant en amide, acide ou ester correspondant ; ou

(ii) dans des conditions de bromation aromatique, suivie de la soumission du dérivé bromo résultant à, respectivement:

(a) un échange lithium-brome, suivi de la réaction du dérivé aryl-lithium avec de l'oxyde d'éthylène pour donner le dérivé 2-hydroxyéthyle, ou
(b) la réaction avec de l'alcool allylique , suivie de l'hydrogénation catalytique de l'alkène pour donner le dérivé 3-hydroxypropyle, ou
(c) la réaction avec le 3-butèn-1-ol, suivie de l'hydrogénation catalytique de l'alkène pour donner le dérivé 4-hydroxybutyle,

et la transformation facultative de l'un quelconque des alcools précités en alcane amine ou nitrile correspondants par activation de leurs groupes hydroxy respectifs pour donner le chlorure ou le mésylate suivie, respectivement, par la réduction, ou la réaction avec une amine de formule R^5R^6NH, ou la réaction avec un cyanure de métal alcalin et la transformation facultative supplémentaire dudit nitrile en amide ou ester correspondants.

(D) alkényle en C_2-C_4 substitué en 2 par CN, $CONR^5R^6$ ou CO_2R^7, ou alkyle en C_2-C_4 substitué en 2 par CN, $CONR^5R^6$, CO_2R^7 ou CH_2NH_2, où R^5, R^6 et R^7 sont tels que précédemment définis dans cette revendication, via le dérivé bromo du (C) (ii) ci-dessus, avec, respectivement, le nitrile, l'amide ou l'ester α,β-insaturé approprié, suivi facultativement par l'hydrolyse de tout ester résultant, la réduction du groupe alkényle résultant et, dans le cas du nitrile, la réduction ultérieure ou concomitante du groupe nitrile en amine primaire correspondante.

(E) alkényle en C_2-C_4 ou alkyle en C_2-C_4, dont chacun est facultativement substitué par CN, $CONR^5R^6$ ou CO_2R^7, où R^5, R^6 et R^7 sont tels que précédemment définis dans cette revendication
via le dérivé bromo de (C) (ii) ci-dessus, avec un réactif d'échange lithium-brome, suivie de la soumission du dérivé aryl-lithium à une formylation, et à la réaction de l'aldéhyde résultant avec le phosphonate ou le sel d'alkyl (en C_1-C_3)phosphonium approprié éventuellement substitué par CN-, $CONR^5R^6$-, ou CO_2R^7-, facultativement suivie de l'hydrolyse de tout ester résultant et de la réduction du groupe alkényle résultant ;
(F) (alcoxy en C_1-C_3)alkyle en C_1-C_2, facultativement substitué par OH ou NR^5R^6 où R^5 et R^6 sont tels que précédemment définis dans cette revendication,

(i) via le dérivé chlorométhyle de (C)(i) ci-dessus, avec soit

(a) un alcanol en C_2 ou C_3, soit
(b) un diol en C_2-C_3, facultativement suivie par l'activation du groupe hydroxy pour donner le mésylate et la réaction soit avec une amine de formule R^5R^6NH, soit avec une amine protégée de formule R^5NHP, R^6NHP ou P'_2NH où P et P' sont tels que précédemment définis dans cette revendication ; ou

(ii) via le dérivé bromo de (C)(ii) ci-dessus, avec un réactif d'échange lithium-brome, suivie de la réaction du dérivé aryl-lithium avec de l'oxyde d'éthylène pour donner le dérivé 2-hydroxyéthyle, et l'activation du groupe hydroxy et la réaction ultérieure comme sous (i) (a) ou (i) (b) ;

(G) $CONR^5R^6$ ou CO_2R^7 où R^5, R^6 et R^7 sont tels que précédemment définis dans cette revendication,
via le dérivé bromo de (C) (ii) ci-dessus, avec un réactif d'échange lithium-brome, suivie par la réaction du dérivé aryl-litihium avec du dioxyde de carbone et la transformation d'une forme convenablement activée de l'acide carboxylique résultant en dérivé amide ou ester par réaction, respectivement, avec une amine de formule R^5R^6NH ou un alcool de formule R^7OH ;
(H) NH_2, halogéno, $NHSO_2NR^5R^6$ ou $NHSO_2R^8$, où halogéno représente fluoro, chloro, bromo, iodo, et R^5, R^6 et R^8 sont tels que précédemment définis dans cette revendication,
dans des conditions de nitration aromatique, suivie de la réduction du composé nitro résultant en amine primaire correspondante et la soumission de ladite amine respectivement à :

(a) une séquence de réaction classique diazotation-halogénation, ou
(b) la réaction avec soit un halogénure de sulfamoyle de formule $R^5R^6NSO_2$halogéno, ou un halogénure de sulfonyle de formule R^8SO_2halogéno, où halogéno est de préférence chloro, soit un sulfamide lorsque R^5 et R^6 représentent tous deux H ;

(I) phényle ou hétérocyclyle, dont l'un ou l'autre est facultativement substitué par méthyle,
via le dérivé bromo de (C) (ii) ci-dessus avec

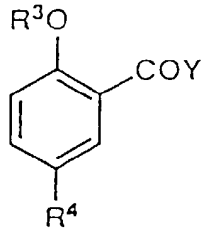
(i) lorsque R^4 est facultativement substitué par phényle ou hétérocyclyle lié via un atome de carbone, le

dérivé zincate phényle ou hétérocyclyle approprié et facultativement substitué en présence d'un catalyseur de palladium, ou :
(ii) lorsque R^4 est un hétérocycle lié via un atome d'azote, l'hétérocycle approprié en présence de cuivre-bronze, d'iode et d'une base ;

suivie dans chaque cas par l'isolation facultative d'un sel pharmaceutiquement acceptable du produit ou la formation d'un tel sel.

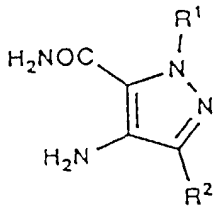
2. Procédé de préparation d'un composé de formule (I) ou d'un sel pharmaceutiquement acceptable d'un tel composé, dans laquelle R^1, R^2, R^3 et R^4 sont tels que précédemment définis dans la revendication 1, qui consiste à faire réagir un composé de formule (II), dans laquelle R^3 représente H, et R^1 et R^2 sont tels que précédemment définis dans la revendication 1, selon l'un quelconque des procédés définis dans la revendication 1, suivi d'une O-alkylation du groupe phénolique pour introduire R^3 et facultativement de l'isolation sous la forme d'un sel pharmaceutiquement acceptable du produit ou de la formation d'un tel sel.

3. Procédé de préparation d'un composé de formule (I), ou d'un sel pharmaceutiquement acceptable d'un tel composé, dans lequel R^1, R^2, R^3 et R^4 sont tels que précédemment définis dans la revendication 1, qui consiste à faire réagir un composé de formule (X) :

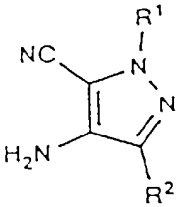


(X)

dans laquelle Y représente chloro ou bromo, et R^3 et R^4 sont tels que précédemment définis dans la revendication 1, avec un aminopyrazole soit de formule (VII) soit de formule (VIII)



(VII)



(VIII)

dans lesquelles R^1 et R^2 sont tels que précédemment définis dans la revendication 1, suivi par la cyclisation des amides résultants respectifs par traitement à l'aide d'une base, facultativement en présence de peroxyde d'hydrogène, et facultativement par l'isolation sous la forme d'un sel pharmaceutiquement acceptable du produit ou par la formation d'un tel sel.

4. Procédé selon la revendication 1, dans lequel :

dans (A), Y représente chloro ou bromo, l'acide de Lewis est le chlorure d'aluminium ou le bromure d'aluminium, et l'agent réducteur est le borohydrure de sodium ;
dans (B), X et Y représentent chloro ou bromo, P représente benzyle et est enlevé par hydrogénation catalytique, et P' représente t-butoxycarbonyle et est enlevé en utilisant du chlorure d'hydrogène ;
dans (C);

(i) la chlorométhylation est mise en oeuvre en utilisant du paraformaldéhyde et de l'acide chlorhydrique

concentré, et

(a) la réduction est effectuée par hydrogénation catalysée au palladium,
(b) l'hydroxyde de métal alcalin est l'hydroxyde de sodium ou l'hydroxyde de potassium,
(c) la réaction avec R^5R^6NH est mise en oeuvre en utilisant un excès de ladite amine,
(d) le cyanure de métal alcalin est le cyanure de sodium ou le cyanure de potassium ;

(ii) la bromation aromatique est mise en oeuvre en utilisant du n-bromosuccinimide et,

(a) l'échange lithium-brome est effectué en utilisant du n-butyl-lithium,
(b) la réaction avec l'alcool allylique est effectué dans des conditions de réaction de Heck,
(c) la réaction avec le 3-butèn-1-ol est effectuée dans des conditions de réaction de Heck ;

dans (D), la réaction avec, respectivement, le nitrile, l'amide ou l'ester α,β-insaturé approprié est effectuée dans des conditions de réaction de Heck en utilisant la tri-o-tolylphosphine, l'acétate de palladium(II) et la triéthylamine, l'hydrolyse facultative de l'ester est effectuée en utilisant une solution aqueuse d'hydroxyde de sodium dans le méthanol, la réduction facultative du groupe alkényle est effectuée par hydrogénation catalysée au palladium, et la réduction facultative ultérieure ou concomitante du groupe nitrile est mise en oeuvre en utilisant du nickel de Raney dans de l'acide acétique glacial ;
dans (E), l'échange lithium-brome est effectué en utilisant du n-butyl-lithium, le réactif de formylation est le diméthylformamide et la réduction de l'alkène est effectuée par hydrogénation catalytique ;
dans (F), la réaction avec

(a) un alcanol en C_2 ou C_3 est mise en oeuvre en présence d'un équivalent de sodium-métal, ou
(b) un diol en C_2 ou C_3 est mise en oeuvre en présence d'un équivalent de sodium-métal, le groupe hydroxy est transformé en son mésylate en utilisant du chlorure de mésyle dans de la pyridine comme solvant, et la réaction avec R^5R^6NH est mise en oeuvre en utilisant un excès de ladite amine, et

(ii) l'échange lithium-brome est effectué en utilisant du n-butyl-lithium :

dans (G), l'échange lithium-brome est effectué en utilisant du n-butyl-lithium et l'acide carboxylique est activé en utilisant un carbodiimide en combinaison avec du 1-hydroxybenzotriazole ;
dans (H), la nitration est effectuée en utilisant de l'acide nitrique concentré en combinaison avec de l'acide sulfurique concentré, le composé nitro est réduit par hydrogénation catalytique, la réaction avec un chlorure de sulfamoyle ou avec un chlorure de sulfonyle est mise en oeuvre en présence d'un excès de pyridine ou de triéthylamine, facultativement en présence de 4-diméthylaminopyridine, et la réaction avec le sulfamide est effectuée à environ 100°C ;
dans (I),

(i) le catalyseur de palladium est le tétrakis(triphénylphosphine)palladium(0) et le dérivé zincate de phényle ou d'hétérocyclyle facultativement substitué est obtenu à partir du dérivé phényle ou hétérocyclyl-lithium correspondant facultativement substitué et de chlorure de zinc anhydre, et
(ii) le composé hétérocyclique est présent en excès et la base est le carbonate de potassium anhydre.

5. Procédé selon la revendication 2, dans lequel la O-alkylation est effectuée en utilisant le chlorure, bromure ou sulfonate d'alkyle approprié en présence de carbonate de potassium.

6. Procédé selon l'une quelconque des revendications 1 à 5, dans lequel R^1 représente H, méthyle ou éthyle ; R^2 représente alkyle en C_1-C_3 ; R^3 représente alkyle en C_2-C_3 ; R^4 représente alkyle en C_1-C_2 facultativement substitué par OH, NR^5R^6, $CONR^5R^6$ ou CO_2R^7 ; acétyle facultativement substitué par NR^5R^6 ; hydroxyéthyle substitué par NR^5R^6 ; éthoxyméthyle facultativement substitué par OH ou NR^5R^6 ; CH=CHCN ; $CH=CHCONR^5R^6$; $CH=CHCO_2R^7$; CO_2H ; $CONR^5R^6$; Br ; NR^5R^6 ; $NHSO_2NR^5R^6$; $NHSO_2R^8$; ou pyridyle ou imidazolyle dont l'un ou l'autre est facultativement substitué par méthyle ; R^5 et R^6 sont chacun indépendamment choisis entre H, méthyle ou éthyle, ou pris ensemble avec l'atome d'azote auquel ils sont liés forment un groupe pipéridino, morpholino, 4-(NR^9)-1-pipérazinyle ou imidazolyle, ledit groupe étant facultativement substitué par méthyle ou hydroxy ; R^7 représente H ou t-butyle ; R^8 représente méthyle ou $CH_2CH_2CH_2NR^5R^6$; et R^9 représente H, méthyle, benzyle, 2-hydroxyéthyle ou acétyle.

7. Procédé selon la revendication 6, dans lequel R^1 représente méthyle ; R^2 représente n-propyle ; R^3 représente éthyle ou n-propyle ; R^4 représente $CH_2NR^5R^6$, $CH_2OCH_2CH_2NR^5R^6$, $CH_2OCH_2CH_3$, $CH_2OCH_2CH_2OH$, $COCH_2NR^5R^6$, $CH(OH)CH_2NR^5R^6$, $CH{=}CHCON(CH_3)_2$, $CH{=}CHCO_2R^7$, CO_2H, $CONR^5R^6$, Br, $NHSO_2NR^5R^6$, $NHSO_2CH_2CH_2CH_2NR^5R^6$, 2-pyridyle, 1-imidazolyle ou 1-méthyl-2-imidazolyle ; R^5 et R^6 pris ensemble avec l'atome d'azote auquel ils sont liés forment un groupe pipéridino, 4-hydroxypipéridino, morpholino, 4-(NR^9)-1-pipérazinyle ou 2-méthyl-1-imidazolyle ; R^7 représente H ou t-butyle ; et R^9 représente H, méthyle, benzyle, 2-hydroxyéthyle ou acétyle.

8. Procédé selon la revendication 7, dans lequel le composé de formule (I) produit est choisi parmi :

la 5-[2-éthoxy-5-(1-méthyl-2-imidazolyl)phényl]-1-méthyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one ;
la 5-[2-éthoxy-5-(4-méthyl-1-pipérazinylcarbonyl)-phényl]-1-méthyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one ;
la 5-[5-(4-acétyl-1-pipérazinyl)acétyl-2-éthoxy-phényl]-1-méthyl-3-n-propyl-1,6-dihydro-7H-pyrazolo-[4,3-d]pyrimidin-7-one ;
la 5-(2-éthoxy-5-morpholinoacétylphényl)-1-méthyl-3-n-propyl-1,6-dihydro-7H-pyrazolo-[4,3-d]pyrimidin-7-one ; et
la 5-(5-morpholinoacétyl-2-n-propoxyphényl)-1-méthyl-3-n-propyl-1,6-dihydro-7H-pyrazolo-[4,3-d]pyrimidin-7-one, et leurs sels pharmaceutiquement acceptables.